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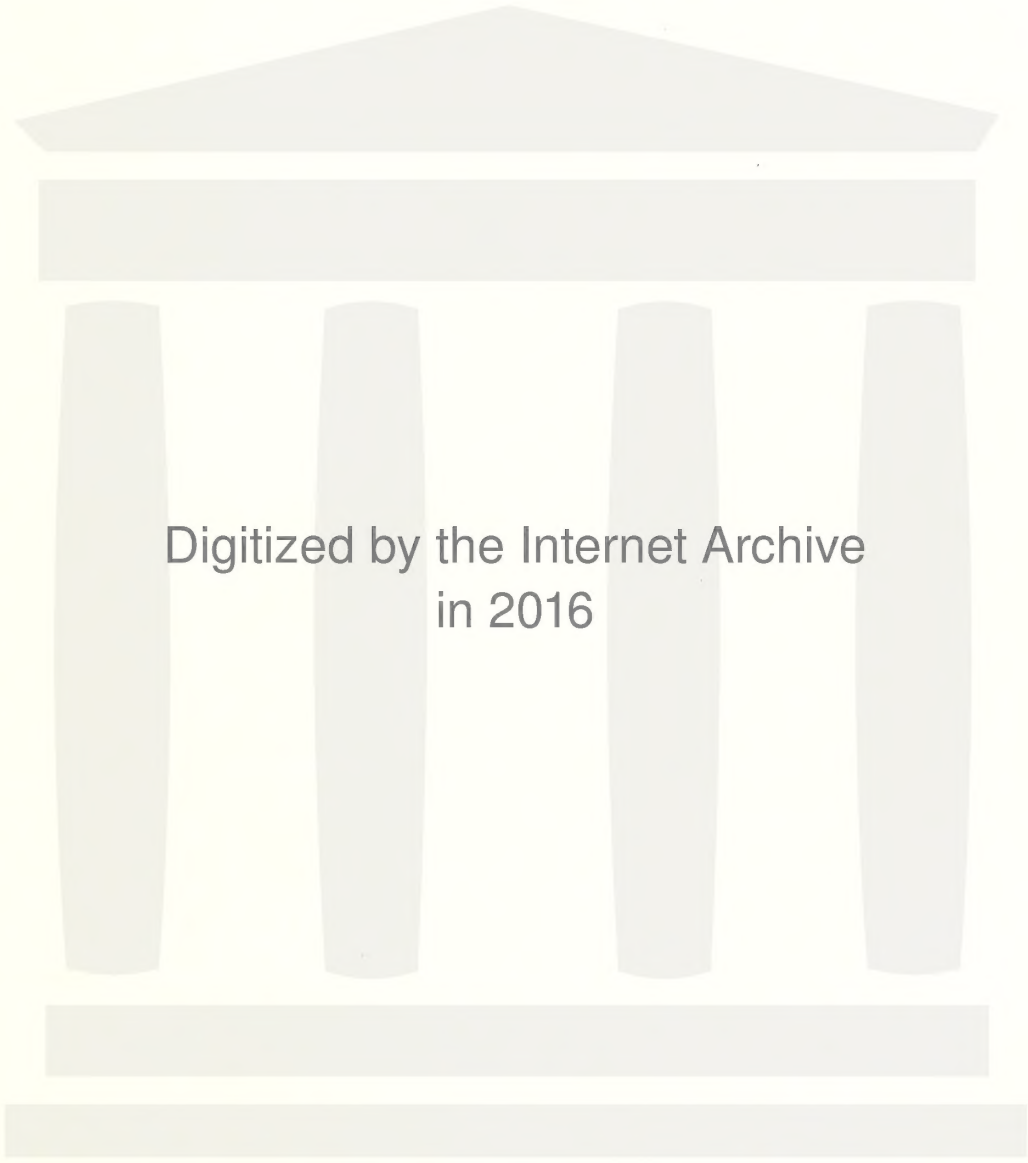
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THE WESTERN Journal of Medicine

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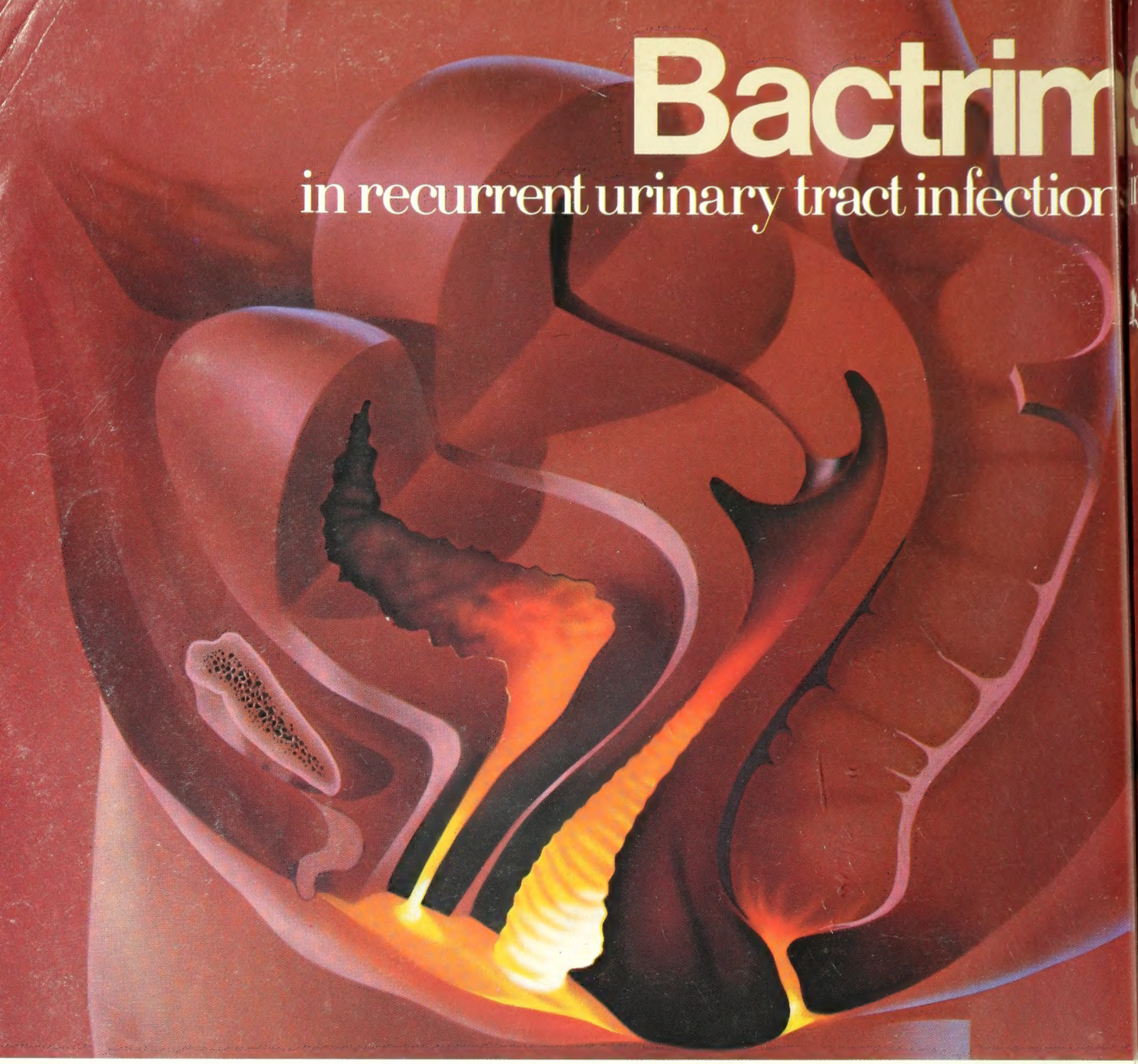

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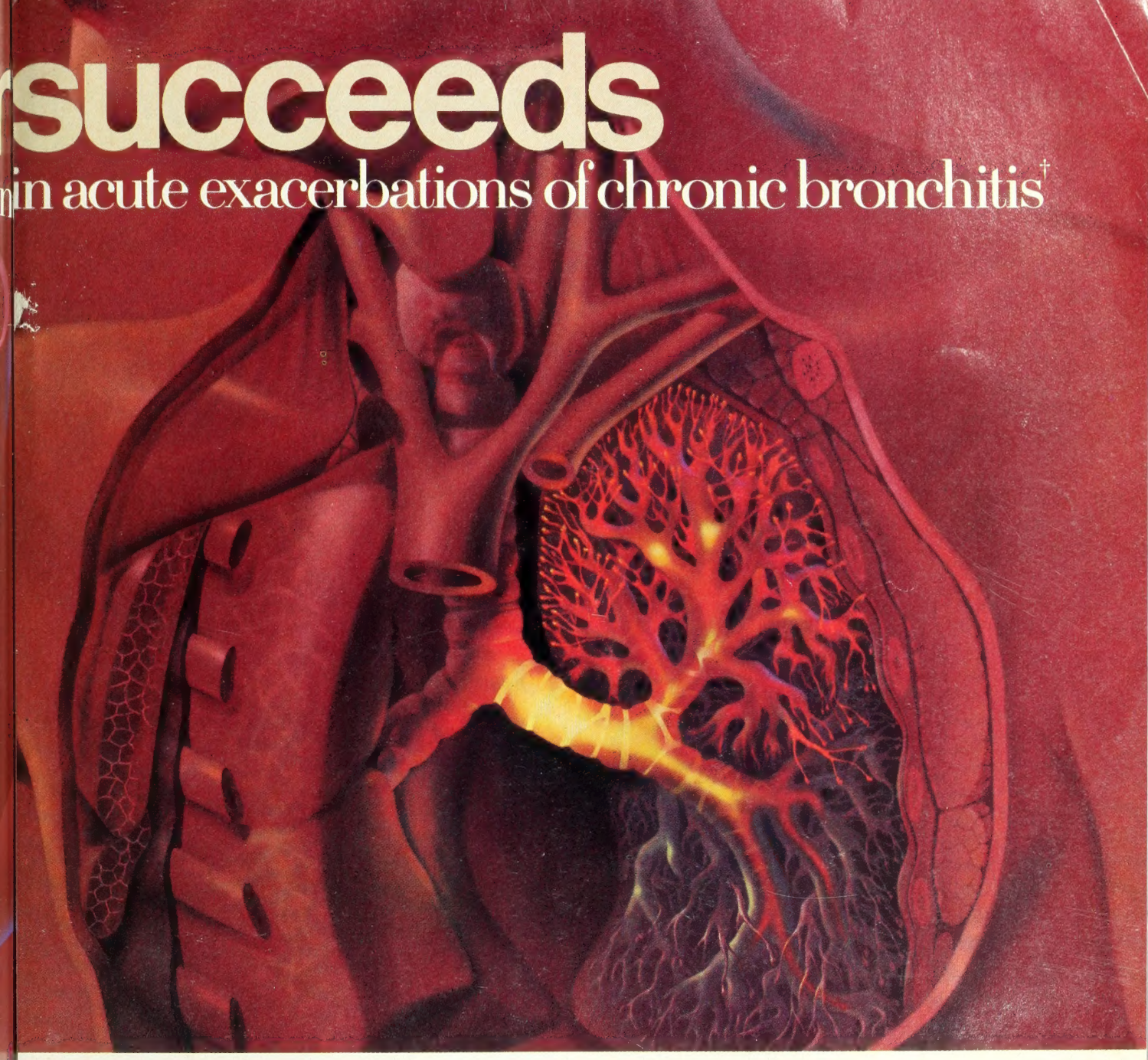

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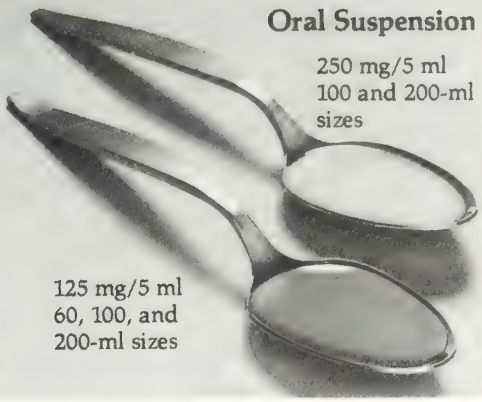

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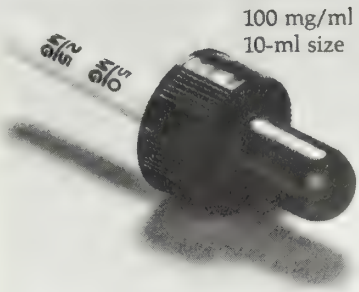

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A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.

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Items of progress in preventive medicine and public health. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

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54 *Medical Problems in Homosexual Men* SELMA K. DRITZ, MD

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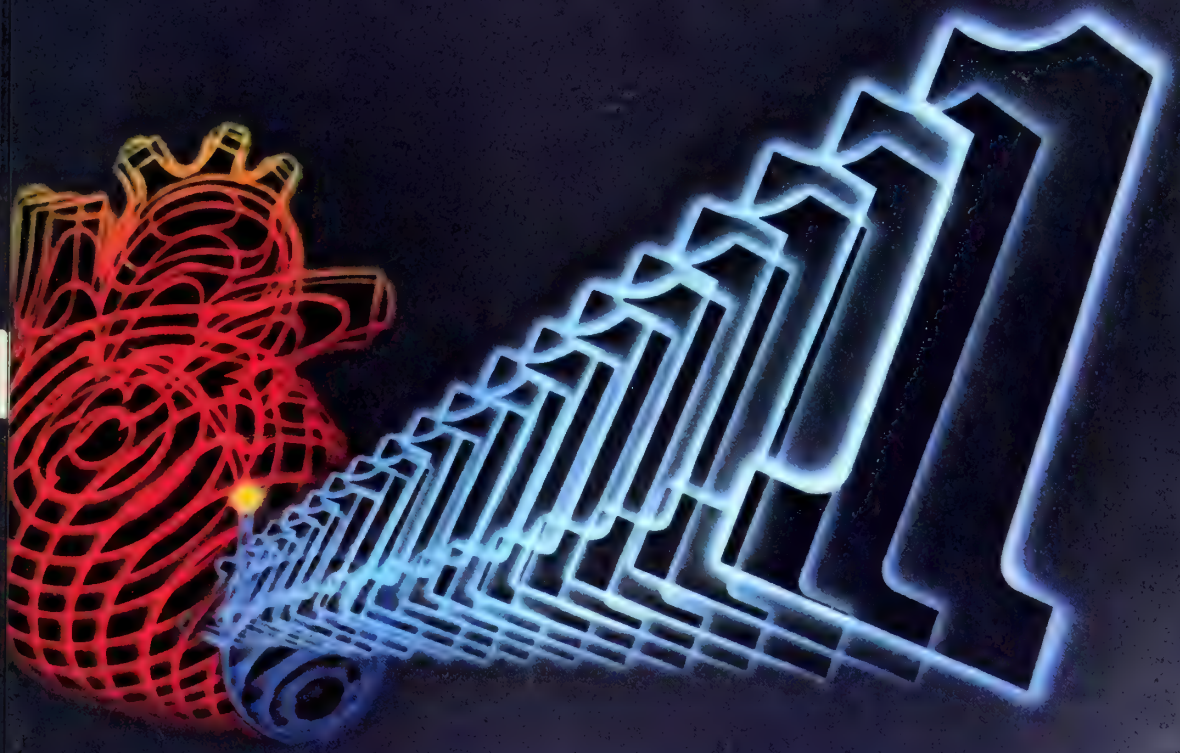

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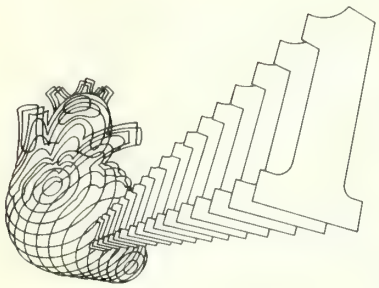

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WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

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Theophylline: no evidence of tolerance.

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Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established. This is, unfortunately, true for most anti-asthmatic medications. Therefore, use of theophylline in pregnant women should be balanced against the risk of uncontrolled asthma
Precautions: THEO-DUR TABLETS SHOULD NOT BE CHEWED OR CRUSHED. Theophyllines should not be administered concurrently with other xanthine medications. It should be used with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, and in the elderly, particularly males, and in neonates. Great caution should be used in giving theophylline to patients in congestive heart failure since these patients show markedly prolonged theophylline blood level curves. Use theophylline cautiously in patients with history of peptic ulcer. Theophylline may occasionally act as a local irritant to G.I. tract, although gastrointestinal symptoms are more commonly central and associated with high serum concentrations above 20 mcg/ml
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References:
1 Theo-Dur package insert
2 Plummer AL *Chest 73*:6 (Suppl 949-957), 1978
3 Jenne J et al *J Allergy Clin Immunol 59* 383-390, 1977
4 Data on file, Key Pharmaceuticals, Inc

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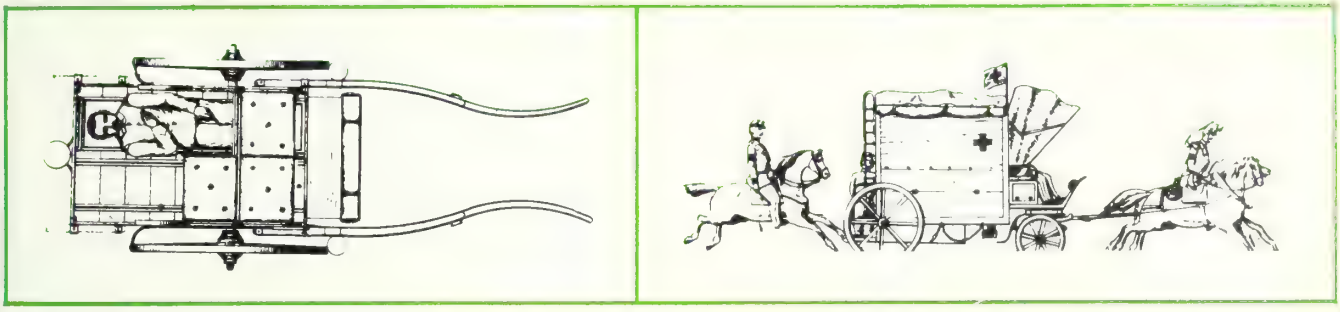

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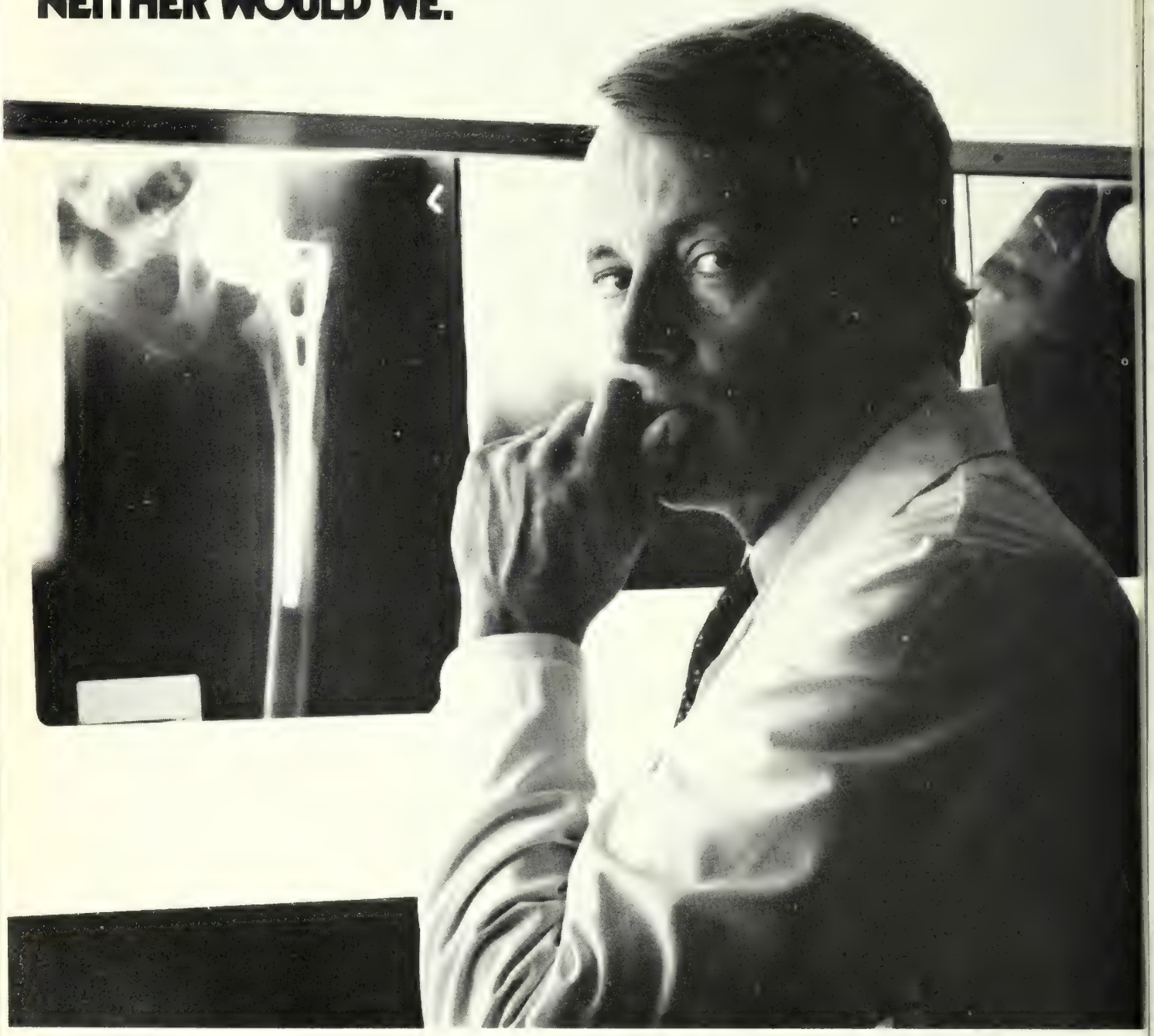

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ANESTHESIOLOGY

January 29-31—**20th Annual Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Fndn., Childrens Hospital of Los Angeles, at Marriott, Los Angeles. Friday-Sunday. 15 hrs. $185. Contact: Wayne Herbert, MD, Prog. Dir., Pediatric Anesthesiology Fndn., P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

March 14-18—**International Anesthesia Research Society—56th Congress.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: International Anesthesia Research Soc., 3645 Warrensville Center Rd., Cleveland, OH 44122. (216) 295-1124.

March 17-21—**American Society of Regional Anesthesia.** Del Monte Hyatt, Monterey. Wednesday-Sunday. 16 hrs. $175. Contact: Gale Thompson, MD, ASRA, P.O. Box 11083, Richmond, VA 23230. (804) 358-0305.

March 21-26—**Anesthesiology 1982—8th Annual Winter Meeting.** Anesthesiology Educational Foundation at Sierra Nevada Inn, Mammoth Lakes. Sunday-Friday. Contact: AEF, P.O. Box 24230, Los Angeles 90024.

April 3-10—**10th Obstetric Anesthesia Conference.** Dept. of Anesthesiology, Ohio State Univ. College of Medicine, at Sheraton Waikiki, Oahu, Hawaii. One week. 25 hrs. Contact: Dept. of Anesthesiology, c/o Bradford Travel, 1200 W. Henderson Rd., Columbus, OH 43220. (614) 457-9990 or (614) 421-8487 (OSU).

CANCER

January 29-31—**Midwinter Oncology Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Diane L. Johnson, L.A. Radiological Soc., P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

February 13—**Gynecological Cancer: Diagnosis and Treatment.** San Francisco Regional Cancer Foundation at Fireman's Fund Bldg., San Francisco. Saturday. 4 hrs. $20. Contact: Terry Sheehy, PhD, S.F. Regional Cancer Fndn., 14th Ave. and Lake St., San Francisco 94118. (415) 221-2132.

February 17—**Advances in Cancer Detection.** Hospital of the Good Samaritan at Biltmore Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Bonnie VanWaardenburg, Cancer Symp., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

February 24-26—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF. Wednesday-Friday.

February 27-28—**Breast Cancer: Conservation Surgery and Radiation Therapy Now—17th Annual San Francisco Cancer Symposium.** West Coast Cancer Fndn.; Am. Cancer Soc., Calif. Div.; St. Mary's Hosp. and Med. Ctr. at Sheraton Fisherman's Wharf, San Francisco. Saturday-Sunday. 12 hrs. $115 before Jan. 1; $140, thereafter. Contact: West Coast Cancer Fndn., 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

April 3—**Oncology Update 1982.** Northridge Hospital Medical Center at Biltmore Hotel, Los Angeles. Saturday. 8 hrs. $125. Contact: Sandra Rozzen, Med. Ed. Dept., NHMC, 18300 Roscoe Blvd., Northridge 91328. (213) 885-5311.

April 22-24—**Bladder Cancer.** American Urological Assn. at Biltmore Hotel, Los Angeles. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, AUA Office of Education, P.O. Box 25147, Houston, TX 77005.

EMERGENCY MEDICINE

January 18-22—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

January 23-30—**Controversies and Problems in Emergency Medicine.** UCSD at Hawaii. One week.

January 25-29—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

(Continued on Page 23)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

When she can't manage, you can.

The sweats. The hot flushes. The distress and discomfort of atrophic vaginitis. The possibility of osteoporosis.* The menopause.

For many women, it's a time of confusion and frustration. Counseling can help her overcome these feelings. But counseling can't stop moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard bone loss*... the true signs of estrogen deficiency. And that's where she needs you most.

You're an expert at estrogen replacement. You know why it should be used. When it's best avoided. That it's not intended to treat nervous symptoms or depression associated with the menopause. That it can be very helpful in treating symptoms related to estrogen deficiency. You know how to cycle therapy. Determine dosage. Check for contraindications and possible complications. Follow-up. You know when therapy should begin, and when it deserves to end.

Most of all, you know your patient—and when she really needs the effective relief you can give her with PREMARIN.

When it comes to managing the estrogen-deficiency symptoms of the menopause, you've got what it takes.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

Prescribed with care by physicians who care.

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg/0.625 mg/1.25 mg/2.5 mg

Please see following page for Brief Summary of Prescribing Information.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1 ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year[1-3] This risk was independent of the other known risk factors for endometrial cancer These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4 5 to 13 9 times greater than in nonusers The risk appears to depend on both duration of treatment[1] and on estrogen dose[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration.[3] It therefore appears prudent to utilize such a regimen Close clinical surveillance of all women taking estrogens is important In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses

2 ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare[5,6] This risk has been estimated as not greater than 4 per 1000 exposures' Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects[13-16] One case control study[16] estimated a 4 7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000 In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U S P) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol equilenin, and 17α-dihydroequilenin as salts of their sulfate esters

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows

Effective:

1 Moderate to severe *vasomotor* symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions)
2 Atrophic vaginitis
3 Kraurosis vulvae
4 Female hypogonadism
5 Female castration
6 Primary ovarian failure
7 Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease
8 Prostatic carcinoma—palliative therapy of advanced disease
9 Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium physiotherapy and good general health-promoting measures Final classification of this indication requires further investigation

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen-dependent neoplasia 3 Known or suspected pregnancy (See Boxed Warning) 4 Undiagnosed abnormal genital bleeding 5 Active thrombophlebitis or thromboembolic disorders 6 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy)

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users.[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives.[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use They should be used with caution in patients with cerebral vascular or coronary artery disease Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed Conditions influenced by fluid retention such as asthma epilepsy, migraine, and cardiac or renal dysfunction, require careful observation Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc Oral contraceptives appear to be associated with an increased incidence of mental depression[2,38] Patients with a history of depression should be carefully observed Preexisting uterine leiomyomata may increase in size during estrogen use The pathologist should be advised of estrogen therapy when relevant specimens are submitted If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete

The following changes may be expected with larger doses of estrogen

a Increased sulfobromophthalein retention
b Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3 increased norepinephrine-induced platelet aggregability
c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered
d Impaired glucose tolerance
e Decreased pregnanediol excretion
f Reduced response to metyrapone test
g Reduced serum folate concentration
h Increased serum triglyceride and phospholipid concentration

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary s nce many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion, cystitis-like syndrome, tenderness, enlargement, secretion (of breasts), nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression chorea, increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females

DOSAGE AND ADMINISTRATION: 1 *Given cyclically for short term use only* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0 3 to 1 25 mg or more daily)

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (*e g* three weeks on and one week off)

Attempts to discontinue or taper medication should be made at three to six month intervals

2 *Given cyclically* Female hypogonadism Female castration Primary ovarian failure Osteoporosis

Female hypogonadism—2 5 to 7 5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration If bleeding does not occur by the end of this period, the same dosage schedule is repeated The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U S P), 2 5 to 7 5 mg daily in divided doses, for 20 days During the last five days of estrogen therapy, give an oral progestin If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding

Female castration and primary ovarian failure—1 25 mg daily, cyclically Adjust upward or downward according to response of the patient For maintenance, adjust dosage to lowest level that will provide effective control

Osteoporosis (to retard progression)—1 25 mg daily, cyclically

3 *Given for a few days* Prevention of postpartum breast engorgement—3 75 mg every four hours for five doses, or 1 25 mg every four hours for five days

4 *Given chronically* Inoperable progressing prostatic cancer—1 25 to 2 5 mg three times daily

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U S P) No 865—Each *purple* tablet contains 2 5 mg in bottles of 100 and 1,000 No 866—Each *yellow* tablet contains 1 25 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 867—Each *red* tablet contains 0 625 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 868—Each *green* tablet contains 0 3 mg in bottles of 100 and 1,000

PHYSICIAN REFERENCES: 1 Ziel, H K, *et al* N Engl J Med *293*:1167-1170, 1975 2 Smith, D C, *et al* N Engl J Med *293*:1164-1167, 1975 3 Mack, T M, *et al* N Engl J Med *294*:1262-1267, 1976 4 Weiss, N S, *et al* N Engl J Med *294*:1259-1262, 1976 5 Herbst, A L, *et al* N Engl J Med *284*:878-881, 1971 6 Greenwald, P, *et al* N Engl J Med *285*:390-392, 1971 7 Lanier, A, *et al* Mayo Clin Proc *48*:793-799, 1973 8 Herbst, A, *et al* Obstet Gynecol *40*:287-298, 1972 9 Herbst, A, *et al* Am J Obstet Gynecol *118*:607-615, 1974 10 Herbst, A, *et al*: N Engl J Med *292*:334-339, 1975 11 Stafl, A, *et al*: Obstet Gynecol *43*:118-128, 1974 12 Sherman, A I, *et al* Obstet Gynecol *44*:531-545, 1974 13 Gal, I, *et al*: Nature *216*:83, 1967 14 Levy, E P, *et al* Lancet *1*:611, 1973 15 Nora, J, *et al* Lancet *1*:941-942, 1973 16 Janerich, D T, *et al*: N Engl J Med *291*:697-700, 1974 17 Boston Collaborative Drug Surveillance Program N Engl J Med *290*:15-19, 1974 18 Hoover, R, *et al*: N Engl J Med *295*:401-405, 1976 19 Daniel, D G, *et al*: Lancet *2*:287-289, 1967 20 The Veterans Administration Cooperative Urological Research Group J Urol *98*:516-522, 1967 21 Bailar, J C Lancet *2*:560, 1967 22 Blackard, C, *et al*: Cancer *26*:249-256, 1970 23 Royal College of General Practitioners: J R Coll Gen Pract *13*:267-279, 1967 23a Royal College of General Practitioners: Oral Contraceptives and Health, New York, Pitman Corp, 1974 24 Inman, W H W, *et al*: Br Med J *2*:193-199, 1968 25 Vessey, M P, *et al*: Br Med J *2*:651-657, 1969 26 Sartwell, P E, *et al*: Am J Epidemiol *90*:365-380, 1969 27 Collaborative Group for the Study of Stroke in Young Women: N Engl J Med *288*:871-878, 1973 28 Collaborative Group for the Study of Stroke in Young Women: J A M A *231*:718-722, 1975 29 Mann, J I, *et al*: Br Med J *2*:245-248, 1975 30 Mann, J I, *et al*: Br Med J *2*:241-245, 1975 31 Inman, W H W, *et al* Br Med J *2*:203-209, 1970 32 Stolley, P D, *et al* Am J Epidemiol *102*:197-208, 1975 33 Vessey, M P, *et al*: Br Med J *3*:123-126, 1970 34 Greene, G R, *et al*: Am J Public Health *62*:680-685, 1972 35 Coronary Drug Project Research Group: J A M A *214*:1303-1313, 1970 36 Mays, E T, *et al*: J A M A *235*:730-732, 1976 37 Pfeffer, R I, *et al*: Am J Epidemiol *103*:445-456, 1976

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(Continued from Page 19)

February 5-6—**Base Station Physician Symposium.** Calif. Chapter, Am. College of Emergency Physicians, at Ahwahnee Hotel, Yosemite. Friday-Saturday. 9 hrs. $125, ACEP members; $150, nonmembers. Contact: CAL/ACEP, 8639 Lincoln Blvd., #240, Los Angeles 90045. (213) 776-1820.

February 7-12—**Winter Sports Injuries.** See Of Interest to All, February 7-12.

February 12-13—**Toxicologic and Infectious Disease Emergencies.** UCLA. Friday-Saturday.

February 20—**Trauma Radiology for the Emergency Practitioner.** Calif. Chap., American College of Emergency Physicians, at St. Mary Medical Center, Long Beach. Saturday. 8 hrs. $75. ACEP members; $95, nonmembers. Contact: CAL/ACEP, 8639 Lincoln Blvd., Suite 240, Los Angeles 90045. (213) 776-1820.

February 28-March 5—**Emergency Medicine.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

March 7-10—**Sports Injuries Update.** UCD at Hyatt, Lake Tahoe. Sunday-Wednesday.

March 14-19—**Third Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Lakes. Sunday-Friday. 25 hrs. $290. Contact: Medical Conferences, Inc., P.O. Box 52-B, Newport Beach 92662. (714) 540-9876.

March 15-19—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Islandia Hotel, San Diego. Monday-Friday. 36 hrs. $425.

April 10-17—**Pediatric Emergencies.** UCSD at Kauai, Hawaii. One week. 21 hrs. $325.

April 24-May 2—**Emergency Medicine.** USC at Hawaii. One week. 25 hrs. $425.

May 10-14—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD. Monday-Friday. 36 hrs. $425.

MEDICINE

January 16-23—**Nephrology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $425.

January 20-23—**Conference on Nephrology and Hypertension.** UCSD at Hilton, San Diego. Wednesday-Saturday.

January 27-29—**Echocardiography: An Introductory Course for the Practicing Physician.** American College of Cardiology and UCLA at Beverly Hilton Hotel, Beverly Hills. Wednesday-Friday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

January 28-30—**All About Peptic Diseases.** American College of Physicians at San Diego. Thursday-Saturday. Contact: ACP, Registrar, 4200 Pine St., Philadelphia 19104. (215) 243-1200.

January 29-30—**Cardiac Rehabilitation.** International Medical Education Corp. at Hyatt Wilshire, Los Angeles. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

January 29-31—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

February 2-6—**What Is Ahead in Lung Diseases for the 80's.** USC at Death Valley. Tuesday-Saturday.

February 3-5—**Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 4-5—**American College of Physicians—Regional Meeting.** Hawaiian Village Hotel, Honolulu. Thursday-Friday. Contact: Robert A. Nordyke, MD, 2013 Kakela Dr., Honolulu 96822.

February 12-13—**Advanced Seminars in Cardiovascular Disease.** Donald N. Sharp Memorial Hospital and Scripps Clinic and Research Foundation at Vacation Village, San Diego. Friday-Saturday. Contact: Nomi Feldman, Conf. Coordinator, 3770 Tansy, San Diego 92121. (714) 453-6222.

February 12-13—**Rheumatology Medicine.** UCD. Friday-Saturday.

February 16-19—**Clinical Investigation.** See Of Interest to All, February 16-19.

February 17-19—**Recent Advances in Noninvasive Cardiac Imaging: Applications in the Diagnosis and Management of Ischemic Heart Disease.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

February 18-20—**Controversies and Problem Solving With Endoscopy—An Update.** So. Calif. Society for Gastrointestinal Endoscopy at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 18 hrs. Contact: Dr. Albert Dreskin, 13652 Cantara St., Panorama City 91402.

February 20-27—**Cardiology.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 21-23—**Recent Advances in Clinical Endocrinology.** UCSF. Sunday-Tuesday.

February 24-25—**American College of Physicians—Regional Meeting.** Hilton, Beverly Hills. Wednesday-Thursday. Contact: Mitchel D. Covel, MD, 9730 Wilshire Blvd., Beverly Hills 90212.

February 25-28—**Federation of the Western Societies of Neurological Science.** Hotel del Coronado, Coronado. Thursday-Sunday. 15 hrs. Contact: Renee Kaseff, 525 Hurlingham Ave., San Mateo 94402. (415) 344-9082.

February 26—**A Day in Nephrology.** Sutter Community Hospitals at Holidome Convention Center, Sacramento. Friday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

February 26-27—**American College of Physicians—Regional Meeting.** Doubletree Inn, Monterey. Friday-Saturday. Contact: Jerry P. Lewis, MD, 618 Francisco Place, Davis 95616.

February 26-28—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Aladdin Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

February 27-28—**Immunology.** STAN. Saturday-Sunday. 12 hrs. $225.

February 27-28—**Basic Neuroscience.** STAN. Saturday-Sunday. 12 hrs. $225.

February 27-28—**Asthma: Impact and Strategies for Change.** UCLA. Saturday-Sunday. 14 hrs. $85.

March 3-6—**Third World Congress for Bronchology.** World Assn. for Bronchology and American College of Chest Physicians at Town and Country, San Diego. Wednesday-Saturday. $250, WAB and ACCP members; $300, nonmembers. Contact: ACCP, P.O. Box 93826, Chicago 60670. (312) 698-2200.

March 3-6—**Immunology and the Clinical Practice of Allergy—6th Annual Course.** UCSD at Hilton Hotel, San Diego. Wednesday-Saturday. 20 hrs.

March 3-6—**Third World Congress for Bronchology.** American College of Chest Physicians and World Assn. for Bronchology at Town and Country Hotel, San Diego. Wednesday-Saturday. $250, ACCP and WAB members; $300, nonmembers. Contact: ACCP, P.O. Box 93826, Chicago 60670. (312) 698-2200.

March 5—**Diabetes.** UCD at Red Lion Inn, Sacramento. Friday.

March 7-10—**Basic Cardiology for the Practicing Physician.** UCSF at Lake Tahoe. Sunday-Wednesday.

(Continued on Page 39)

SPOT-RESISTANT
ORAL CONTRACEPTION
IS HERE!
It's LO/OVRAL 30. And here's how it holds spotting and breakthrough bleeding to a minimum: Hormone balance right from the start...and throughout the cycle. Hormone balance made possible with a very low dose oral contraceptive because of the supportive progestational activity of norgestrel, Wyeth's exclusive progestogen.
Regular withdrawal bleeding, too
despite its low dose. In clinical trials amenorrhea—defined as absence of bleeding in the 7 pill-free days—was reported in only 2.1% of total cycles. And when defined as absence of bleeding for 60 days or more (as it often is), the incidence was only 0.2%.*
And comfort for most patients*
thanks to the same balance that helps prevent spotting and breakthrough bleeding. In the clinical trials, most patients stayed free of common side effects such as nausea (0.6% of cycles), vomiting (0.1%), depression (0.5%) and acne (0.9%).
Wyeth Laboratories
Philadelphia, Pa 19101
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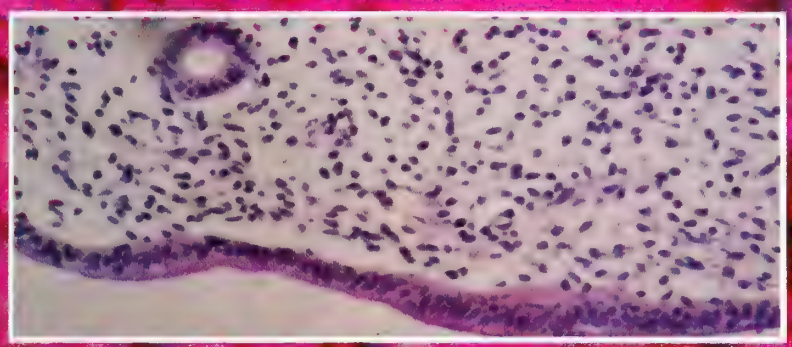
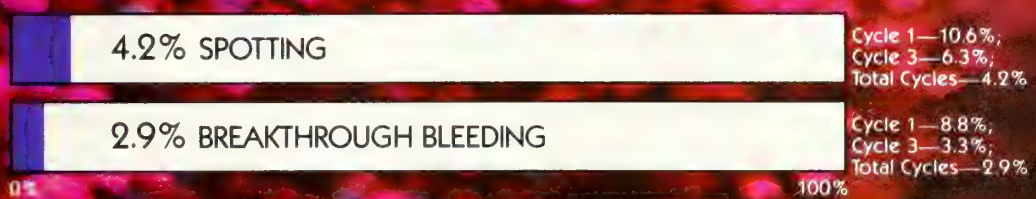


LO/OVRAL—1st cycle
Biopsy of intact endometrium in stable, progestogen suppressed state. Small, tubular gland in loose stroma without hemorrhage, fragmentation or debris characteristic of desquamating endometrium.

Even in the first cycle, the effective action of LO/OVRAL on the endometrium, such as you see here, provides the resistance against spotting and breakthrough bleeding you hope to achieve.

HISTOLOGICALLY... AND CLINICALLY.



A near-spotless record— in clinical trials involving 22,489 cycles*

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. Contraindications, Warnings, Precautions, Adverse Reactions, etc., in the accompanying In Brief should be carefully considered.

See full prescribing information.

LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth

...with a near-spotless record!

See important information on following page.

IN BRIEF:

Indications and Usage— LO OVRAL ® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders 3. Cerebral-vascular or coronary-artery disease 4. Known or suspected carcinoma of the breast 5. Known or suspected estrogen-dependent neoplasia 6. Undiagnosed abnormal genital bleeding 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000, ages 35-44—33/100,000, ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately

A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia, papilledema, or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline

Carcinogenesis—See Warnings on carcinogenic potential of OC's

Pregnancy—Category X. See Contraindications, Warnings

Nursing Mothers—See Warnings

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: Gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema, chloasma or melasma which may persist, breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease), change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, cholestatic jaundice; migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates; vaginal candidiasis, change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

LO/OVRAL® each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol

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Motrin® vs aspirin w/codeine...
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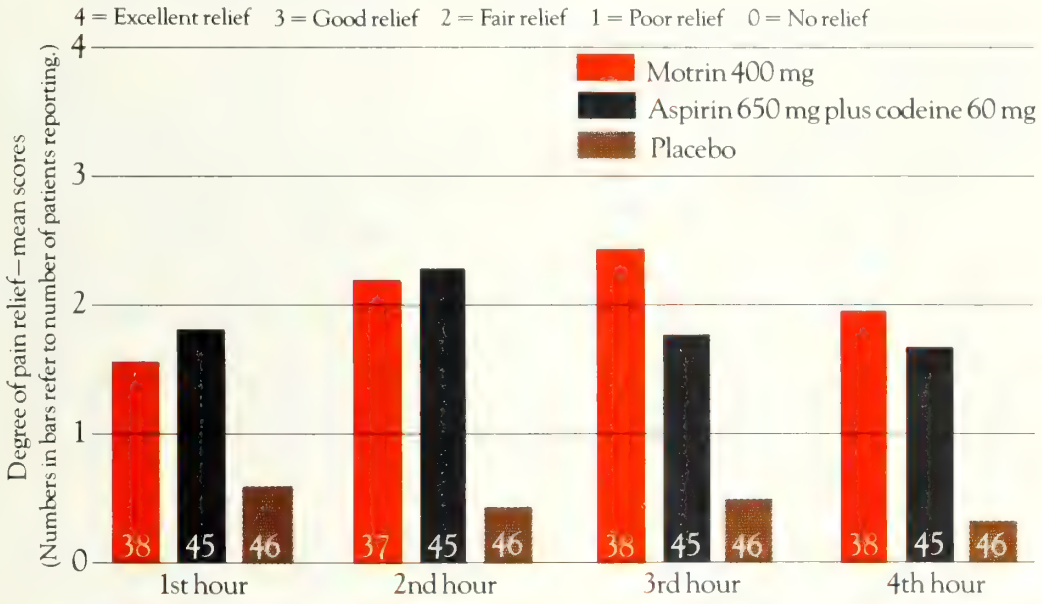
compare the analgesic effect

A *Motrin* 400 mg dose relieved postsurgical dental pain as effectively as a combination of 650 mg aspirin and 60 mg codeine (two aspirin-with-codeine No. 3 tablets) in a study of 129 patients. In this double-blind, placebo-controlled, randomized study, no statistically significant difference in relief of pain was noted at 1, 2, and 4 hours between the *Motrin* and aspirin-with-codeine groups... with *Motrin* being significantly more effective ($p = 0.03$) at the three-hour interval. Active treatment was significantly more effective ($p < 0.0001$) than placebo at all time intervals.

Comparison of pain relief
Motrin vs aspirin-codeine combination



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One tablet q4-6h prn
For relief of mild to moderate pain:

Motrin® 400 mg TABLETS
ibuprofen, Upjohn

• Not a narcotic • Not addictive • Not habit forming • Nonscheduled • Acts peripherally • Relieves pain rapidly • Relieves inflammation • Indicated in acute and chronic pain • Well tolerated (The most common side effect with *Motrin* is mild gastrointestinal disturbance.)

Please turn the page for a brief summary of prescribing information.

Upjohn

Motrin® (ibuprofen) now proved an effective analgesic for mild to moderate pain

Motrin® Tablets (ibuprofen, Upjohn)

Indications and Usage: Relief of mild to moderate pain

Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin:* Used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy nor by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal (4% to 16%). This includes nausea;* epigastric pain;* heartburn;* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness;* headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis, including flares of chronic disease: Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for relief of pain.

Do not exceed 2400 mg per day.

Caution: Federal law prohibits dispensing without prescription.

For additional product information, see your Upjohn representative or consult the package insert.

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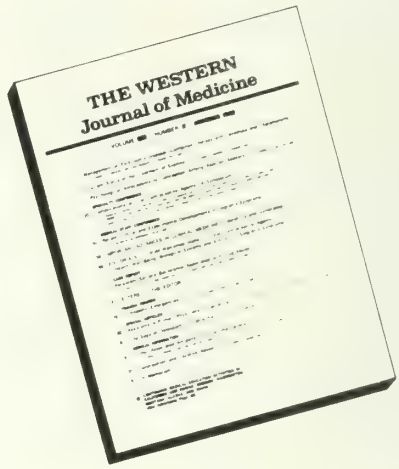
MARCH 1981

THE WESTERN Journal of Medicine



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INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 731 Market Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format, and to give close attention to syntax, grammar and spelling.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed double-spaced throughout (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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Journal Articles

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1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 292:444-456, Apr 26, 1978

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 7: 76-79, Sep 1978

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, IL, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, MA, Publishing Sciences Group, Inc, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia. American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

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Refer to: Smith FE, Mann JM: Pneumococcal pneumonia: Experience in a community hospital. West J Med 136:1-5, Jan 1982

Pneumococcal Pneumonia: Experience in a Community Hospital

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Cases of patients admitted to hospital with community-acquired pneumonia over a three-year period were reviewed to determine whether pneumococcal pneumonia and pneumococcal bacteremia occurred as frequently as reported in urban and university-based studies. Pneumococcus was isolated in only 25 of 202 patients (12 percent) in whom adequate attempts at culture were made, only one patient had documented pneumococcal bacteremia and no patients died of pneumococcal pneumonia proved by culture. Prospective studies in community hospitals should be considered to define more clearly the epidemiology of pneumococcal pneumonia in the nonurban United States population. These studies would also contribute to a rational policy for use of pneumococcal vaccine in this country.

Streptococcus pneumoniae (pneumococcal) pneumonia is generally considered a major cause of community-acquired bacterial pneumonia requiring admission of the patient to hospital. For example, in a study from Grady Hospital in Atlanta[1] a specific bacterial pathogen was identified in 57 percent of cases, and the pneumococcus was judged responsible for 62 percent of these bacterial pneumonias. The Grady study documented a 19 percent mortality among patients with pneumococcal pneumonia; of those with bacteremic pneumococcal pneumonia, the mortality was 32 percent, compared with 6 percent for nonbacteremic patients. According to a standard medical textbook, bacteremia occurs in 20 percent to 30 percent of pneumococcal pneumonia cases.[2] In the PraCon study, it was estimated that in 1976 pneumococcal pneumonia accounted for 82 percent of hospital admissions for pneumonia,[3] and the incidence of pneumococcal pneumonia has been estimated to range from 21 to 230 cases per 100,000 population each year.[4] These and similar statistics emphasize the importance of pneumococcal pneumonia and have been used in making decisions about the potential benefits of immunization with pneumococcal vaccine, which was licensed in November 1977.

In the past, studies of the cause and prognosis of pneumonia have generally been done in large urban hospitals. We questioned whether data

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derived from urban areas would accurately reflect the pneumococcal pneumonia experience in a small community or rural hospital setting. We reviewed the records of all patients with pneumonia admitted to Los Alamos Medical Center during a three-year period (January 1, 1976, through December 31, 1978) to identify the cause of pneumonia and its associated mortality.

Patients and Methods

Los Alamos is located in the Jemez Mountains of northern New Mexico, at an altitude of 7,500 feet (2,300 m). The mid-1977 county population was 17,100. The community is relatively isolated geographically, the nearest towns being 20 and 40 miles away, so that few residents seek medical care elsewhere for acute illnesses. In addition, residents of the nearby Rio Grande Valley who work in Los Alamos often seek care in Los Alamos; 40 percent of all patients admitted to hospital live outside Los Alamos County. Therefore, the lower bound of the study population is estimated at 17,000 and the upper bound at 25,000. This population stems from several racial and ethnic backgrounds from all over the United States, with a predominance of non-Hispanic whites and many Hispanic New Mexicans. Native Americans, who receive care at Indian Health Service hospitals, are rarely admitted to the Los Alamos Medical Center.

The community is served by a single 88-bed hospital. In 1977 the medical population of Los Alamos included 28 physicians, all board-certified. Seven internists, one family practitioner and six pediatricians provided most primary care to the community.

The Los Alamos Medical Center laboratory is directed by a board-certified pathologist and the bacteriology procedures are done by certified medical techniques (MT-ASCP). Standard culture techniques are carried out according to a procedure manual, with internal quality control standards. The laboratory participates in the quarterly review of the College of American Pathologists Laboratory Survey Program to Extent 4.

Coding in the hospital medical records department includes listing of both primary and secondary diagnoses. All records in which pneumonia, bronchopneumonia, pneumonitis or related terms were listed as an admission or discharge primary or secondary diagnosis were identified for study. Each record was reviewed and those meeting the criteria for pneumonia were included in the study.

Criteria for pneumonia were as follows: (1) an abnormal chest roentgenogram diagnostic of pneumonia—for example, acute parenchymal infiltrate or segmental or lobar consolidation; (2) clinical abnormalities consistent with pneumonia, such as fever, rales, physical finding of consolidation in the lung; (3) exclusion of other causes of these abnormalities in the judgment of the attending physician. For each patient, data were obtained on age, sex, race, dates of admission and discharge from hospital, onset of pneumonia, chest roentgenograms, preceding antibiotic therapy, underlying conditions and outcome. Sputum Gram stain, sputum culture, transtracheal aspirate, lung biopsy or blood cultures obtained before antibiotic therapy were reviewed for microbiologic data.

After reviewing all records, patients younger than 5 years old at the time of illness were excluded because few microbiologic studies had been done to identify a causal agent in those patients. Patients who were admitted to hospital without pneumonia and in whom pneumonia then developed after three days or longer were considered to have a nosocomial infection. Because this study was undertaken to review pneumonia acquired in the community, these patients were also excluded.

The case definition for pneumococcal pneumonia required identification of *S pneumoniae* in blood specimens or transtracheal aspirate or isolation of heavy growth in sputum culture.

Results

A total of 325 patients in hospital met the criteria for pneumonia. Of this number, 91 patients were younger than 5 years old and four patients had nosocomial infections. Of the remaining 230 patients, ages ranged from 6 to 98 years, with a mean of 54 years and a median of 57 years of age. Of these, 117 of the patients were male and 113 were female. The mean duration of the hospital stay was 9.3 days (median 8 days), with a range of 2 to 36 days. Thirteen of these patients (6 percent) died.

A reasonable attempt had been made to identify a causative organism in 202 patients (88 percent of total). Sputum culture had been done in 165

patients, blood specimens were cultured in 95 patients, transtracheal aspiration was done on 13 patients and bronchoscopy in 6 patients. An open-lung biopsy procedure was done in one patient. The quality of the sputum specimens submitted for culture was difficult to evaluate, since Gram stains were not always done. Organisms associated with pneumonia in the 202 patients are shown in Table 1.

Peripheral blood leukocyte count and differential were reviewed but varied widely and were not helpful in distinguishing community-acquired viral from bacterial pneumonia.

S pneumoniae was isolated in 25 patients (12 percent of 202 pneumonia cases). One patient had blood cultures positive for pneumococcus, one patient had pneumococcus isolated from a transtracheal aspirate and 23 patients had a sputum culture with heavy growth of pneumococcus. In the patient with pneumococcal bacteremia,

TABLE 1.—*Culture Data in 202 Pneumonia Patients, 1976 Through 1978, Los Alamos, New Mexico*

Organism	Type of Clinical Specimen				Total
	Sputum N (%)	Transtracheal Aspirate	Bronchoscopy	Blood	N (%)
Streptococcus pneumoniae	23 (11)*	1	..	1	25 (12)
Klebsiella	12 (6)	..	..	..	12 (6)
Escherichia coli	6 (3)	..	..	..	6 (3)
Proteus	3 (1)	..	1	..	4 (2)
Staphylococcus aureus	3 (1)	..	1	1	5 (2)
Enterobacter	2 (1)	..	..	..	2 (1)
Hemophylus influenzae	1	1	..	..	2 (1)
Bacteroides corrodens	1	..	..	1	2 (1)
Aspergillus	1†	..	..	..	1
Coccidioides immitis	..	..	1	..	1
No growth	113 (56)	11 (5)	3 (1)	92 (46)	219
Total positive versus Total specimens	52/165	2/13	3/6	3/95	60/279

*Number of specimens positive for the organism (percentage of all 202 patients with specimen positive for that organism).

†Patient with lung biopsy procedure.

TABLE 2.—*Comparison of Patients With Pneumococcal Pneumonia and Patients With Nonpneumococcal Pneumonia (Total of 202 Patients), Los Alamos, New Mexico*

Characteristic	Pneumococcal Pneumonia Group (N = 25)	Nonpneumococcal Pneumonia Group (N = 177)
Age	Mean = 58.3 years Median = 55 years	Mean = 55.9 years Median = 57 years
Sex Male	15	84
Female	10	93
Length of hospital stay	Mean = 9.7 days Median = 9 days Range = 3-23 days	Mean = 9.8 days Median = 8 days Range = 2-36 days
Underlying disease:		
None	8	66
Heart disease	6	48
Asthma	2	11
Chronic obstructive pulmonary disease	4	27
Alcoholism	3	9
Malnutrition	1	4
Cancer	1	8
Dementia	..	6
Other neurological disease	1	8
Diabetes	1	14
Trauma	1	8
Preceding upper respiratory infection	1	20
Renal failure	..	4
Miscellaneous	..	12

sputum cultures did not grow pneumococcus. Four patients with pneumococcus identified on sputum culture were found to have an additional organism in notable quantity.

Ages among the patients considered to have pneumococcal pneumonia ranged from 24 to 87 years, with a mean of 58.3 years and a median of 55 years. Eight of these patients had no known underlying disease. Table 2 correlates patients with pneumococcal pneumonia and patients with all other types of pneumonia. Although pneumonia was considered the cause of death in 13 patients, no patient with identified pneumococcal pneumonia died while in hospital.

Based on a population of 20,000 for the three-year observation period, the 25 cases of pneumococcal pneumonia represent an incidence rate of 42 cases per 10^5 person-years.

Discussion

The difficulty of identifying the etiologic organism in cases of pneumonia is well known. For pneumococcal pneumonia technical difficulties in isolating pneumococcus from the sputum may occur, and, alternatively, the pneumococcus may colonize the nasopharynx, leaving unsuspected the organism actually causing pneumonia. In 1971 a study from San Diego[5] showed that in 23 of 51 patients (45 percent) with bacteremic pneumococcal pneumonia, no pneumococci were identified in cultures of sputum or nasopharynx. Sensitive techniques for collecting sputum (for example, transtracheal aspiration or bronchoscopy) may be less available in a community hospital than in a university hospital. Because no pathologic organism was identified in 68 percent of all patients from whom sputum was obtained, the adequacy of sputum culture can certainly be questioned in our study. However, while only 11 percent of sputum specimens were positive for *S pneumoniae* by culture, the pneumococcus was still the most commonly isolated bacterial pathogen in the pneumonia patients enrolled in this study.

Bacteremia is said to occur in 20 percent to 30 percent of cases of pneumococcal pneumonia.[2] If bacteremia had occurred in 20 percent to 30 percent of the cases in this study, a total of 11 pneumococcal pneumonia cases would be the expected number among 202 patients. In 25 patients in whom pneumococcal pneumonia was confirmed, 11 patients had blood cultures, only one of which yielded *S pneumoniae*. Therefore, the rate of bacteremia, that is, 9 percent, is lower than the 20 percent to 30 percent rate that is generally cited.

The proportion of pneumonia cases caused by *S pneumoniae* in this study is much lower than the PraCon estimates or the prospective study results from Grady Hospital. More important, none of the patients from whom pneumococcus was isolated died. We are unable to determine the extent to which patients with pneumococcal pneumonia may not have been admitted to Los Alamos Hospital Medical Center or were admitted elsewhere; while this would alter the incidence rate of all pneumococcal pneumonia in the community, it is unlikely that a bias in favor of admitting patients with less severe cases, with less bacteremia and resultant lower mortality, would have occurred.

The licensure of pneumococcal vaccine in late November 1977 could have resulted in widespread use of this vaccine with lower rates of pneumococcal pneumonia in the community in 1978 compared with 1976 through 1977. However, there was no evidence of a decline in hospital cases of pneumococcal pneumonia; seven cases occurred in 1976, nine cases in 1977 and nine cases in 1978. Pneumococcal vaccine was used by Los Alamos physicians in 1978, but in the absence of information on pneumococcal vaccination rates in Los Alamos, we cannot assess the effect of vaccine on serotypes responsible for pneumonia. In any case, none of the patients with pneumococcal pneumonia in this study had received pneumococcal vaccine before the onset of illness.

Pneumococcal vaccine has been advocated for the prevention of pneumococcal pneumonia in patients at high risk of acquiring pneumonia or of dying if pneumonia should occur. The use of pneumococcal vaccine for persons at increased risk of pneumococcal pneumonia (for example, asplenic patients) seems appropriate. Further, the use of vaccine in populations epidemiologically at higher risk for disease may be reasonable in populations similar to those served by large urban or university hospitals, based on rates of incidence and mortality as reported from Grady Hospital in 1972. However, our data suggest a lower incidence of patients admitted with pneumococcal pneumonia to hospital. This study of community hospital experience can be useful in defining major policy issues in pneumococcal vaccination, as there is insufficient information about the epidemiology of pneumococcal pneumonia in nonurban populations.[6] Studies of larger populations may

be needed to document and clarify differences between urban university hospital and small community hospital experience with pneumococcal pneumonia.

Recommendations

The following recommendations are offered: (1) Several larger community hospitals should review their pneumonia data for comparison with urban and university hospital data. (2) From these studies, an attempt should be made to define high-risk patients in order to provide practical guidance for identification of persons most likely to benefit from pneumococcal vaccination.

REFERENCES

1. Sullivan RJ, Dowdle WR, Marine WM, et al: Adult pneumonia in a general hospital: Etiology and host risk factors. Arch Intern Med 129:935-942, 1972

2. Hook EW: Pneumococcal pneumonia, *In* Beeson PB, McDermott W, Wyngaarden JB (Eds): Textbook of Medicine, 15th Ed. Philadelphia, WB Saunders, 1979, p 349

3. Roden DR, Platt WG: A Study to Estimate the Prevalence and Costs of Pneumonia. Fairfax, VA, PraCon Inc, Feb 1978

4. Fraser DW, Broome CV: Pneumococcal vaccine: To use or not. JAMA 245:498-499, 1981

5. Foy HM, Wentworth B, Kenny GE, et al: Pneumococcal isolations from patients with pneumonia and control subjects in a prepaid medical care group. Am Rev Resp Dis 111:595-603, 1975

6. A Review of Selected Federal Vaccine and Immunization Policies: Based on Case Studies of Pneumococcal Vaccine. Office of Technology Assesssment, Congress of the United States, 1979

Refer to: Bohannon NJ, Zilbergeld B, Bullard DG, et al: Treatable impotence in diabetic patients. West J Med 136: 6-10, Jan 1982

Treatable Impotence in Diabetic Patients

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The incidence of impotence in diabetic men is reported to be almost 50 percent. The prevailing view is that such impotence is due to organic factors. To investigate the validity of this notion we compiled the cases of 34 diabetic men having difficulty in penile erection. Our results suggest that impotency in men with diabetes is psychogenic in many cases and can be treated successfully by brief sex therapy.

THE INCIDENCE OF IMPOTENCY in diabetic men is high—almost 50 percent.[1-4] Although writers are careful to note that difficulty in or absence of erection in diabetic patients can be psychogenic, the impression conveyed is that such problems are generally of organic origin.[5,6] The very fact that impotence is much more frequent among diabetic men than among the general male population serves to strengthen the notion of organic causality.

Few writers[7-13] have challenged the prevailing view. Yet diabetes has an essentially emotional aspect in that it is a chronic, incurable disease that affects all other aspects of the patient's life. Because it is generally agreed that psychological factors are the most common causes of impotence, it is logical to assume that concern of a diabetic patient about his health and its effect on his sexuality could provoke impotence even in the absence of any organic cause. What begins as a simple sexual concern may quickly evolve into iatrogenic impotence if a physician or other health care provider expresses the idea that diabetes is the probable cause of the patient's sexual dysfunction.[13]

We think that the occurrence of organically caused impotence has been greatly exaggerated because of insufficient consideration of emotional factors. If our position is correct, it should follow that many cases of impotence in diabetic patients can be effectively treated by brief sex therapy.

Brief sex therapy has been thoroughly described in the literature,[14-16] and thus needs no elaboration. Most sex counseling for penile erection problems involves helping patients reduce their anxiety about sexual activity and increase their capacity for arousal and pleasure. This is often accomplished by having them focus on the giving and receiving of pleasure without an erect penis. This approach relieves the pressure to have erections: Even if a man does not regain erectile ability through therapy, he may learn other ways of giving and receiving pleasure that are satisfying to him and his partner.[17]

Patient Population

Thirty-four diabetic men treated by the authors or sex therapist colleagues had erection problems. Their ages varied between 22 and 63 years, the

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duration of impotence between 3 months and 9 years, and the duration of the diabetes between 6 months and 24 years. We used these 34 patients as our base population, not because they met the accepted criteria of true impotence, but because they had been told they were impotent, or considered themselves so, and were also diabetic. Most of them had been told that their impotence was irreversible. Nevertheless, they sought sex therapy on their own, in the hope that the alleged irreversibility was not actual. Thus, this group is a selected diabetic population, and not one referred by health professionals because of a suspected psychogenic component of the impotency.

Several patients had signs of peripheral sensory neuropathy but none to our knowledge showed indications of autonomic neuropathy. At least 25 percent had other medical problems, especially heavy drinking and hypertension, and approximately as many were not under good diabetic control. Most had some belief that diabetes caused impotence. More than 50 percent had been told by at least one health professional that probably nothing short of a penile prosthesis would help their erectile impotency. Such statements had been made despite the fact that the extent of the patients' erectile problems varied considerably. Some men had erections but said these erections were not as firm as before. Others could get erections by way of masturbation but not with their partners. Some only had erections on waking in the morning; others said that they had had no morning erections for some time. Many of these patients disregarded erections obtained under situations not explicitly sexual, and for this reason considered themselves impotent—as did their physicians—in spite of the above histories. When a carefully taken history elicits that a patient has strong erections, whatever the circumstances, the conclusion must be that he does not suffer from complete organic impotence due to diabetes—or to anything else.

Treatment and Results

The men were seen in brief therapy sessions, 75 percent with their partners and the rest of them alone, either because they had no partners, because their partners refused to participate or because they did not want their partners included. Therapy lasted from 1 to 16 sessions (average 7 sessions). Our criterion of success was the ability regularly to get erections firm enough for intromission. In several cases where the men did not have partners or their partners would not allow sexual intercourse, success had to be estimated—a justified mode of judgment inasmuch as our interest was primarily to determine how many of our patients could be helped to have erections through brief therapy.

By our standard of success, therapy was effective for 28 of the 34 men (about 83 percent). Three brief case studies are presented to give a clear understanding of some of the issues encountered in treating diabetic men, specifically for sexual problems.

Case 1. A 49-year-old man had been diabetic for 15 years. He was a heavy drinker and diabetic control was poor. He had been married for 23 years, during the last 5 of which he had been unable to get erections with his wife. For this and other reasons the marriage was in jeopardy. The patient had several times attempted to have sexual relations with other women but could not get an erection. By masturbating he sometimes obtained a partial erection after much effort. He said he had had no spontaneous morning erection in the past year. Three physicians told him that nothing but a penile prosthesis could help him but this solution did not appeal to him.

The treatment lasted for nine sessions and focused on two issues: helping the marital relationship and relieving the tremendous pressure this patient felt in sex.[18] His wife refused to participate in the therapy, but he was given suggestions for developing greater closeness with her. He was also given suggestions for being more relaxed during masturbation and other sexual activity. Before the end of therapy the patient was having full erections in masturbation and sexual intercourse. Unfortunately, his marriage remained strained, although satisfying sexual activity was now sometimes possible. A year and a half later, he divorced his wife and soon began another relationship based primarily on sexual attraction. That relationship has since ended, but three years after termination of therapy this patient still functions well sexually.

Case 2. A 38-year-old man had been diabetic for three years. He took insulin and diabetic control was good. He had not had erections with his wife for more than a year but this was not considered a problem because she was not interested in sexual relations. He came to treatment because of complete inability to attain erections with a woman with whom he had been having an affair for several months. He reported weak morning erections and slightly fuller ones from masturbation.

Therapy consisted mainly of helping the patient

to understand the situations he needed to have erections (for example, assurance of privacy, being more comfortable with his partner and feeling less pressure to satisfy her through intercourse). He was also given some suggestions for relaxing during masturbation. In his second and last appointment, three weeks later, he reported full erections with masturbation and greater comfort with his woman friend—the result of their discussing her sexual expectations. He called a few weeks later to say he was having regular erections and enjoyable sexual intercourse.

CASE 3. An 81-year-old man, married for the first time at age 70, had had a satisfactory sex life for five years when his ability to get erections began to deteriorate. When he came to treatment he had not had erection from self-stimulation or on waking for more than a year. He suffered from a number of medical problems, including diabetes of 12 years' duration, chronic obstructive pulmonary disease and angina. He had avoided sexual contact with his wife for more than a year because "I can't do her any good"; moreover, because of his shyness about approaching sexual questions, he had been unable to discuss the problem with her. Finally he found the courage to tell his physician. He was given an injection of testosterone without benefit.

This patient was seen twice. He was encouraged to discuss his concerns with his wife. Specific suggestions recommended nondemanding pleasure-giving exercises. The couple was able to talk about sex for the first time in their marriage and enjoyed the touching exercises. The talking and touching helped the patient to feel more relaxed. He learned that "we can have fun when I put my mind to it." He reported several partial erections firm enough for intercourse. He hoped they would get even fuller in the future, but whether or not that happened he was pleased with the sexual closeness he now felt with his wife.

Discussion

Impotence and diabetic neuropathy are often linked in the literature[19] without a clear distinction between peripheral sensory neuropathy and peripheral autonomic neuropathy.[20,21] Although it is true that impotence can be caused by diabetic autonomic neuropathy, this should not be considered the case unless such a neuropathy can be objectively demonstrated and measured in abnormalities other than the single manifestation of impotence.[22] These abnormalities often include the symptoms of postural hypotension, nausea or vomiting or both (due to gastroparesis diabeticorum), overflow incontinence or recurrent urinary tract infections (due to neurogenic bladder), sweating abnormalities (including nocturnal sweating not associated with hypoglycemia, gustatory sweating or defective sweating with body heating), persistent tachycardia or diabetic diarrhea (sometimes alternating with periods of constipation).[23]

On the other hand, the symptoms of peripheral sensory neuropathy common among diabetic patients (numbness, tingling, pain, "woody feeling," "crawling sensation" or itching, usually affecting the toes, feet and legs first) usually do not contribute to organic sexual dysfunction. The distinction between peripheral sensory neuropathy and autonomic neuropathy is thus important, and unwarned health professionals may misinterpret the presence of peripheral sensory neuropathy alone as sufficient to cause impotence.

A person with Type II diabetes (adult onset) with no complications other than mild background retinopathy or a peripheral sensory neuropathy would be unlikely to have organic impotence caused by diabetes. For autonomic neuropathy to be implicated, a patient must show objective findings of its presence, plus of course the absence of full erections at any time. Tests that reflect the presence of autonomic neuropathy include: (1) cystometrography, (2) decreased cardiovascular response to Valsalva's maneuver,[24-27] (3) blood pressure response to sustained hand grip,[28] (4) latent bulbocavernosus reflex response,[29] (5) absent or decreased sensation of testicular pain[20] and (6) sweating responses to food ingestion or body heating.[30,31] In the absence of any of these criteria, one would strongly suspect a psychological cause for the complaint of impotence.[24]

The more numerous the manifestations of autonomic neuropathy—especially bowel or bladder problems—the more likely the relationship of the impotence to this process. However, the effects of autonomic neuropathy on a patient's self-esteem may contribute to self-doubt regarding sexual adequacy and to concomitant development of psychogenic impotence. Studies have shown that some patients with objective evidence of autonomic neuropathy, as shown by the above-mentioned tests, still have adequate erectile competence for satisfactory intercourse.[22]

Deutsch and Sherman[32] recently suggested that unrecognized diabetes is a cause of secondary impotence among a large percentage of men. Their

study reflects a major problem in that there was a substantial age difference between those men with secondary impotence and both the normal group and the group with premature ejaculation. Comparisons regarding incidence of diabetes among men who have not been matched by age are not valid because there is a significant increase in incidence of diabetes after age 40.[33] Indeed, 70 percent of diabetic persons are diagnosed at age 40 or later. Deutsch and Sherman's normal group had a mean age of 37.1 years, whereas the secondary impotence group had a mean age of 47.2 years. This finding suggests that a larger percentage of older men would be diabetic, regardless of what the presenting complaint was.[34]

The Emotional Impact of Diabetes

The emotional impact of diabetes has not been given enough weight when considering the sexual life of diabetic persons. People with diabetes are aware that they have a shortened life expectancy, that they must be careful about food, drink and exercise, and that incapacitating complications such as blindness or gangrene may develop.

Emotional variables such as anxiety, anger and depression have been shown to cause and perpetuate penile erection problems.[35] Because the influence of these factors has been discussed in detail elsewhere,[14-16] we will note only that their effect may be cumulative. A man concerned about his health or general adequacy may be adversely affected by what he construes as hostility, criticism or lack of satisfaction on the part of his partner.

Many diabetic persons seeking help for erection problems focus so heavily on their disease that they become convinced they cannot have erections. Some physicians contribute to this belief.[13] One of our patients commented about the effects of discussion with several physicians, "Going to bed with the idea that your sickness may not allow you to have an erection just doesn't make for good sex."

Many older men, diabetic and nondiabetic, are involved in an erection-equals-virility-equals-masculinity stereotype. If they cannot achieve an erection, they feel finished as sexual beings. They may not have engaged in mutual touching and caressing of the genitals with their partners as part of their regular sexual patterns. For many of them, foreplay is nonexistent. Their inability to get erections may leave them with feelings of shame, guilt, discouragement and frustration. They may give up trying to have sexual relations altogether, assuming that without erections they cannot satisfy themselves or their partners.

Results of Brief Sex Therapy

Diabetic men with presumed organic impotence have been shown to respond well to either psychiatric intervention or treatment in a sex dysfunction clinic. Renshaw has recently presented some results of the latter.[13] Three men with diabetes of a duration from 8 to 20 years who had been told by their internists that sex therapy would be a waste of time and money (and who had additional medical problems—such as clinical depression, heavy drinking, cirrhosis and hypertension) were nevertheless treated successfully in four to seven weeks, with their wives' participation. Four years later they all continued to feel satisfied with their sexual function.

A more optimistic outlook than that generally conveyed by the current literature is warranted. Renshaw[36] reported that of 15 cases recently having had brief sex therapy, 14 were successful. Our own results with 28 of 34 patients confirm the possibility of such a high rate of success.

Case reports in themselves are insufficient to validate or invalidate any hypothesis, and we are by no means suggesting that no diabetic men suffer from organic impotence. But our results and Renshaw's are clear: At least some men thought to have diabetes-caused impotence have benefited greatly from brief therapy. We urgently need controlled research to determine more about the effects of diabetes on sexual functioning.

Conclusion

The use of brief sex therapy with diabetic men complaining of impotence can have positive effects —even if erectile ability does not return. As men learn how to relax more, to give up damaging myths that contribute to poor sexual self-esteem and to explore various parts of their bodies capable of sensual and sexual stimulation, they discover ways of being sexual that satisfy them and their partners.

Finally, the process of brief sex therapy can also serve as an evaluative, learning and screening tool for patients contemplating insertion of a penile prosthesis. Many diabetic men are offered this option as soon as they complain of impotence to a physician. Sex therapy can further differentiate between psychogenic and organic impotence and

either spare the patient unnecessary surgical intervention if he is satisfied with the outcome, or help him make an informed decision about such intervention if he is not.

REFERENCES

1. Cooper AJ: The causes and management of diabetes. Postgrad Med 48:549-554, Sep 1972

2. Kolodny RC, Kahn CB, Goldstein HH, et al: Sexual dysfunction in diabetic men. Diabetes 23:306-309, Apr 1974

3. Rubin A, Babbott D: Impotence and diabetes mellitus. JAMA 168:498-500, Oct 1958

4. Schoffling K, Federlin K, Ditschuneit H, et al: Disorders of sexual function in male diabetics. Diabetes 12:519-526, Nov-Dec 1963

5. Ellenberg M: Impotence in diabetes—The neurologic factor. Ann Intern Med 75:213-219, Aug 1971

6. Kent S: Impotence as a consequence of organic disease. Geriatrics 30:155-157, Sep 1975

7. Finkle AL: Male impotence: Brief office therapy. Mind and Medicine 5:1-3, Feb 1978

8. Finkle AL: Psychosexual problems of aging males: Urologist's viewpoint. Urology 13:39-44, Jan 1979

9. Finkle AL: Sexual impotence: I. Urology/sexuality clinic. Urology 16:449-452, Nov 1980

10. Finkle AL: Commentary on male impotence (Correspondence). West J Med 133:256-257, Sep 1980

11. Katz AM: Commentary. Med Asp Human Sex 7:27-28, Apr 1973

12. Renshaw DC: Impotence in diabetics. Dis Nerv System 36:369-371, 1975

13. Renshaw DC: Impotence in diabetics, *In* LoPiccolo J, LoPiccolo L (Eds): Handbook of Sex Therapy. New York, Plenum Press, 1978, pp 433-440

14. Masters WH, Johnson VE: Human Sexual Inadequacy. Boston, Little, Brown and Co, 1970

15. Kaplan HS: The New Sex Therapy. New York, Brunner/Mazel, 1974

16. Zilbergeld B: Male Sexuality. Boston, Little, Brown and Co, 1978

17. Schiavi RC: Psychological treatment of erectile disorders in diabetic patients. Ann Intern Med 92:337-339, Feb 1980

18. Zilbergeld B: Alternatives to couples counseling for sexual problems: Group and individual therapy. J Sex Marital Ther 6: 3-18, Spring 1980

19. Ellenberg M: Sexual function in diabetic patients. Ann Intern Med 92:331-333, Feb 1980

20. Campbell IW, Ewing DJ, Clarke BF, et al: Testicular pain sensation in diabetic autonomic neuropathy. Br Med J 2:638-639, Jun 1974

21. Karacan I: Diagnosis of erectile impotence in diabetes mellitus. Ann Intern Med 92:334-337, Feb 1980

22. Hosking DJ, Bennet T, Hampton JR, et al: Diabetic impotence: Studies of nocturnal erection during REM sleep. Br Med J 2:1394-1396, Dec 1979

23. Editorial: Diabetic autonomic neuropathy. Br Med J 2:2-3, Jul 1974

24. Ewing DJ, Campbell IW, Burt AA, et al: Vascular reflexes in diabetic autonomic neuropathy. Lancet 2:1354-1356, Dec 1973

25. Nathanielsz PW, Ross MB, Ross EJ: Abnormal response to Valsalva maneuver in diabetics. Diabetes 16:462-465, Jul 1967

26. Wheeler T, Watkins PJ: Cardiac denervation in diabetes. Br Med J 4:584-589, Dec 1973

27. Watkins PJ, Mackay JD: Cardiac denervation in diabetic neuropathy. Ann Intern Med 92:304-307, Feb 1980

28. Ewing DJ, Irving JB, Kerr F, et al: Cardiovascular response to sustained handgrip in normal subjects and in patients with diabetes mellitus: A test of autonomic function. Clin Sci Molecular Med 46:295-306, Mar 1974

29. Ertekin C, Reel F: Bulbocavernosus reflex in normal men and in patients with neurogenic bladder and/or impotence. J Neurol Sci 28:1-15, May 1976

30. Watkins PJ: Facial sweating after food: A new sign of diabetic autonomic neuropathy. Br Med J 1:583-587, Mar 1973

31. Goodman JI: Diabetic anhidrosis. Am J Med 41:831-835, Nov 1966

32. Deutsch S, Sherman L: Previously unrecognized diabetes mellitus in sexually impotent men. JAMA 244:2430-2432, Nov 28, 1980

33. Joslin EP, Krall LP: Incidence of diabetes. *In* Joslin EP, Root HF, White P, et al (Eds): The Treatment of Diabetes Mellitus, 10th Ed. Philadelphia, Lea & Febiger, 1959, pp 18-46

34. Kinsey AC, Pomeroy WB, Martin CE: Sexual Behavior in the Human Male. Philadelphia, WB Saunders Co, 1948

35. Zilbergeld B: Myth of men as sex machines. Med Asp Human Sex 13:71-83, Apr 1979

36. Renshaw DC: Interview on the sexually dysfunctional diabetic. Sex Med Today 3:8-38, Feb 1979

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Treatment of Foreign Body Obstruction of the Upper Airway

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The treatment of foreign body obstruction of the upper airway has been the subject of considerable attention and controversy. Current recommendations from the National Academy of Sciences, the American Red Cross and the American Heart Association include the use of back blows, abdominal thrusts (Heimlich maneuver) or chest thrusts (or both) and finger probes, until definitive therapy by trained medical and paramedical personnel becomes available. Nevertheless, a number of authorities on this subject have claimed that these approaches are dangerous, and that abdominal thrusts should be the first and only first-aid technique used in this situation.

There are only limited data on which to make recommendations regarding this issue. Clinical evidence is scanty and of a highly anecdotal and unscientific nature. The data that are available suggest that a combination of maneuvers is in fact preferable to any single maneuver. Experimental physiologic data on both humans and animals tend to support this concept and suggest that back blows, which generate high initial pressures, may dislodge objects from the larynx enough to allow subsequent thrust maneuvers, which generate more sustained increases in intrathoracic pressure, to move the object out of the larynx. At this time, in the absence of definitive data, it seems reasonable to teach as many lay citizens as possible to recognize upper airway obstruction due to foreign body and to perform any and all of these techniques (preferably in combination), as well as external cardiopulmonary resuscitation (CPR) where appropriate, on choking victims.

MUCH ATTENTION has been focused on the treatment of foreign body obstruction of the upper airway. The lay public has long been interested in the problem, to a great extent because of highly publicized comments by Dr. Henry Heimlich that established medical authorities have ignored appropriate treatments and misled the public. Dr. Heimlich,[1] who first proposed the Heimlich maneuver, or "abdominal thrust," in 1974, has made several other eminently quotable statements that have also generated widespread comment. Among these is the claim that back blows, listed by the American Heart Association and the American

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Red Cross as the first treatment modality in upper airway obstruction, are "death blows," and the statement that the various national policy-making committees for these major organizations have engaged in "Watergate cover-ups" to avoid adequate recognition of the Heimlich maneuver.

Interest in this controversy has not been confined to the lay community. Numerous medical groups have sponsored debates regarding the treatment of upper airway obstruction, and official positions have been solicited from a variety of medical organizations. In light of the intense and often strident debate concerning this problem, it is well worth our while to review in detail all the available evidence on this subject.

History

Dr. R. K. Haugen[2] first coined the term "cafe coronary" in 1963 to describe sudden death following aspiration of pieces of meat into the trachea. Haugen noted large pieces of food materials obstructing the airway and generally lodged at the level of the larynx during autopsies of a number of sudden-death victims. Early suggestions regarding emergency treatment of upper airway obstruction ranged from finger-probe maneuvers and use of mechanical devices to manually remove the object from the airway, to slaps on the back, as well as external cardiopulmonary resuscitation (CPR).[2-4] In 1974 Dr. Heimlich described the "Heimlich maneuver," in which the rescuer "rapidly and strongly presses into the victim's abdomen, forcing the diaphragm upward, compressing the lungs, and expelling the obstructing bolus."[5,6] Early recommendations of the American Red Cross and National Academy of Sciences did not include the Heimlich maneuver, or abdominal thrust, among suggested management techniques.[3] In 1976, however, the American Red Cross changed its policy to include the abdominal thrust.[7] They continued to recommend that four rapid back blows be done initially, followed by four abdominal thrusts, with repetition of these sequences as long as the victim remains conscious. They also recommended that, in the presence of unconsciousness, finger probes be attempted. Finally, they recommended the institution of mouth-to-mouth ventilation and CPR in the event of cardiac arrest. Dr. Heimlich has challenged this set of recommendations, asserting that back blows are injurious and deleterious, and that only the Heimlich maneuver should be used.[8,9] He has also asserted that the failure of the American Red Cross to change its recommendations so as to concur with his own represents an attempt by those committee members responsible for the recommendations to "cover up" their earlier refusal to include the Heimlich maneuver and their continued insistence on the back blow.[10]

There are only a limited amount of scientific data available on the subject of the treatment of upper airway obstruction. This article will review the limited clinical and experimental data available, and determine what conclusions can be safely drawn. We will evaluate the substance of Dr. Heimlich's claim that only the Heimlich maneuver should be used. We will also attempt to formulate what recommendations should be made to the general public for the emergency treatment of upper airway obstruction.

TABLE 1.—*Mortality Data—1973 to 1975**

Year	Heart Disease	All Accidents	Automobile Accidents	Suffocation From Ingested Objects
1973	757,075	115,821	55,511	3,013
1974	738,171	104,622	46,402	2,991
1975	716,215	103,030	45,853	3,106

*From Accident Facts.[12]

Etiology—Epidemiology

Deaths from upper airway obstruction caused by food are reported approximately 3,000 times per year in the United States.[6,11,12] Even this number may represent a significant underestimation, since many sudden deaths resulting from

TABLE 2.—*Principal Types of Accidental Deaths, 1973 to 1977**

Year	Ingestion of Food, Object	Motor Vehicle	Falls	Drowning	Fires, Burns	Firearms	Poison (solid, liquid)	Poison by Gas
1973	3,013	55,511	16,506	8,725	6,503	2,618	3,683	1,652
1974	2,513	46,402	16,339	7,876	6,236	2,513	4,016	1,518
1975	3,106	45,853	14,896	8,000	6,071	2,380	4,694	1,577
1976	2,059	47,038	14,136	6,827	6,333	2,059	4,161	1,569
1977	3,000	49,500	14,000	7,100	6,600	2,000	3,900	1,600

Source: National Center for Health Statistics and National Safety Council.

*From Accident Facts—1978 Ed. National Safety Council, Chicago, 1978.

TABLE 3.—*Deaths From Suffocation/Ingested Objects—1975/1976**

Age Range (years)	*No. of Deaths*	*Death Rate (per 100,000)*
0- 4	504	2.9
5-14	77	0.2
15-24	223	0.4
25-34	218	0.8
35-44	241	1.2
45-54	369	1.6
55-64	429	2.4
65-74	451	3.0
75-Up ...	594	5.7
All ages ..	3,106	1.4

*Reproduced from Report on Emergency Airway Management, 1976, with the permission of the National Academy of Sciences, Washington, DC.

upper airway obstruction may not be identified, but rather may be mistakenly ascribed to cardiac disease or other causes. While the recognized total is far smaller than the toll taken by several major causes of death (see Table 1), it is generally equivalent to that of many other important causes of accidental death, including death caused by fires, firearms and poisoning (see Table 2).

Victims tend to be either very young or very old, as shown in Table 3. These figures represent the number of people who die from total obstruction of the airway, generally at the level of the larynx. They do not include the large number of children who aspirate foreign bodies—such as coins, marbles and peanuts—past the larynx, down the trachea and into a mainstem bronchus. Such foreign body aspirations lead to significant pulmonary complications, and can be fatal in some cases. However, pulmonary aspiration of foreign bodies represents a different entity from upper airway obstruction secondary to foreign bodies that are caught at the level of the vocal cords. Those instances in small children of laryngeal obstruction caused by objects such as peanuts or coins are considered in this discussion.

There are several risk factors involved in the precipitation of upper airway obstruction.[2,13] Inebriation significantly enhances the likelihood of such an event. This becomes even more probable statistically when the victim is not only inebriated but has poor eating habits and uses dentures. Most reported cases of upper airway obstruction occur in public restaurants, where victims suddenly collapse following an attempt to swallow large and poorly chewed pieces of meat. A universal choke sign, introduced by Dr. Heimlich in 1974,[5] has been introduced to the public so that a victim will be able to communicate to any onlookers that he is in fact choking.

Physiology

A number of factors influence the prognosis of the victim of food choking. One of these is the site of obstruction of the foreign object.[14] Objects that lodge at the level of the larynx, either at or just above the vocal cords, will allow a reasonable chance of adequate resuscitation. Objects that are lodged just below the vocal cords, or on the under side, are much more difficult to move via any of the techniques described. For these patients, removal with medical instruments, under direct vision, is probably the only reasonable alternative. Unfortunately, very few such victims would survive the time of transport to a medical facility.

The degree of obstruction also plays a critical role in prognosis.[14,15] Partial obstruction allows the passage of some air, and a partially obstructing object is easier to remove. Complete obstruction rapidly produces severe hypoxia, concomitant with much higher pressure requirements for removing the obstructing object. Finally, the size of the object is of course an important factor, as larger objects are more difficult to remove and tend to produce more complete obstruction.[15]

Normal coughing produces large increases in intrathoracic pressure, upper airway flow and tidal volume.[14] The maneuvers we will be discussing, especially back blows, abdominal thrusts and chest trusts, can be thought of as artificial cough techniques intended to generate similar increases in pressure, flow and volume. Dr. Heimlich states that clearance of an obstructing object from the larynx is directly related to the peak flow achieved by his technique.[10] Other investigators claim that the direct pressure to which the object is subjected is responsible for movement of the object,[14] while still others consider the kinetic energy applied to the object to be the determining factor.[16] The question of which factors are important in budging a wedged object is an important one, as the various artificial cough techniques produce widely divergent effects in terms of pressure, flow and volume.

Movement of an object where there is no resistance present is proportional to the amount of force (pressure over a given area) delivered to it. This is likewise related to the total pressure delivered to the object over a period of time, and correlates with the amount and rate of air flow

in the vicinity of the object. In the presence of resistance, however, an object can be moved only if the sudden force generated overcomes the static resistance of the object. Instantaneous increases in pressure proportional to the sudden force delivered are critical if there is any amount of resistance. A wedged object subjected to high pressures over a short period may move a short distance, but then no further if the applied force is removed. On the other hand, small increases in pressure (and thus force) sustained over a long period of time will move a frictionless object a great distance (along with the air around it), but will fail to budge a wedged object if instantaneous force never exceeds the static resistance. We will soon see the importance of these observations in the treatment of upper airway obstruction.

Clinical Data

No controlled prospective studies in the treatment of upper airway obstruction have been reported, nor are any likely to be performed. Because of obvious ethical considerations, analysis of efficacy of various therapeutic techniques must rely on isolated reports sent to scientific organizations by isolated individuals. These reports are by nature not only anecdotal but also retrospective, and generally they reflect the experience of lay rescuers. They also reflect an inherent bias, as civilian reports are more likely to document successful cases than unsuccessful ones. This same type of bias may be reflected by a tendency to ascribe success to a particular procedure among several used when the citizen is reporting a case to the expert who has recommended that procedure.

Furthermore, the inherent difficulties with record keeping and inability on the part of the reporters to distinguish between the effect of individual sequential maneuvers as opposed to combined effects of various maneuvers make it very hard to accurately interpret the results. These reporting limitations are present in each of the reported clinical series on which we will comment.

It is worth emphasizing that anecdotal reporting is notoriously difficult to evaluate, particularly when the reports come from isolated nonprofessional people. The landmark *Journal of the American Medical Association (JAMA)* supplement issue in 1974, devoted to the American Heart Association Protocol for CPR, displays on its cover an entire series of techniques anecdotally reported at various times throughout history to be successful in reviving dead persons.[17] Anecdotal assertions as to the efficacy of Laetrile (*l*-mandelonitrile-β-glucuronic acid) as an antitumor agent, for instance, or of vitamin E for the treatment of a multiplicity of unrelated ailments, have received widespread public attention despite the lack of any scientific evidence. A variety of techniques to resuscitate drowning victims, including rectal fumigation, led to a parade of 2,000 such victims "saved" in England on the first day of the nineteenth century.[18,19] The efficacy of various procedures in the treatment of upper airway obstruction should not be compared to these examples. However, it is important to recognize that anecdotal assertions and sweeping generalizations made on the basis of such anecdotes should be viewed with some degree of caution.

When Heimlich first described his abdominal thrust maneuver in 1974, he called on physicians and members of the lay public to contact him if and when they used, or know of someone else's having used, the Heimlich maneuver. He has subsequently collected a large series of patients from these individual reports sent to him, and has reported results at various times.[5,6,8,9] Dr. Heimlich's reports consistently suggest almost universal efficacy of the Heimlich maneuver, with very limited adverse effects, and these Dr. Heimlich ascribes to misuse of the maneuver rather than to inherently deleterious consequences. Dr. Heimlich has also reported that the authors of a number of these testimonials make the claim that other maneuvers, such as the "back blow," were unsuccessful with patients whose obstruction was subsequently relieved by the abdominal thrust.

A similar experience was reported by Dr. Trevor Hughes, whose series of 428 cases of food choking has been summarized in an abstract of scientific papers for the American Society of Anesthesiologists (and later expanded to 536 cases).[20] Hughes' results are very similar to Heimlich's, but this is perhaps not surprising as over 90 percent of Dr. Hughes' cases were supplied by Dr. Heimlich. None of the cases were gathered by Dr. Hughes himself.

The Emergency Cardiac Care Committee of the American Heart Association also collected a series of 225 victims of food choking, treated with various artificial cough techniques.[21] The findings in this series were evaluated by Dr. Joseph Redding in the July 1979 issue of *Critical Care Medicine*.[22] Dr. Redding warns, as do the statisticians of the American Heart Association itself, that it is difficult to interpret the material they

gathered (R. Britten, personal communication). This is because the material was gathered retrospectively, on the basis of individual ancedotal reports, with considerable problems of record keeping. Several data forms were used and many answers were either illegible or ambiguous. Other questions were not answered. Perhaps the most important drawback was that the forms contain no mechanism for rescuers to distinguish between combined effects of various maneuvers and individual effects of sequential maneuvers. Many correspondents marked several measures as having been simultaneously successful, while others marked only one maneuver as successful (ostensibly the last maneuver employed). Of 225 total cases, success was attributed to one method in 116 cases in which only that method was used. In 29 cases, several methods were noted to be successful, while in 75 other cases, several maneuvers were used but only one was marked successful.

Because multiple successes were occasionally reported with individual victims, a total of 256 successes were noted, with 130 failures, on only 225 victims (see Table 4). Attempts were made to analyze the results both when multiple successes were included in the series and when these cases were excluded, so that only success unequivocably related to the single maneuver marked successful would be counted. The final data, with all the reservations that we must ascribe to it, seem to demonstrate that back blows are moderately successful (around 50 percent), while the abdominal thrust and chest thrust are much more successful (70 percent to 85 percent). Interestingly, external CPR had the highest rate of success (86 percent) in a small number of trials (14).

Each of the maneuvers was marked successful in at least several cases where it was the only maneuver employed. Furthermore, each of the maneuvers was marked successful in cases where one or all of the other maneuvers were marked unsuccessful (see Table 5). There were 38 cases where the Heimlich maneuver was considered successful after the back blow had ostensibly failed. On the other hand, there were 14 instances where the back blow was considered life-saving after the Heimlich maneuver had been considered to have failed. A similar pattern was seen for all of the maneuvers in all the various combinations.

Finally, there is some suggestion that in many of the cases it may have been the combination of maneuvers that dislodged the foreign body. This is difficult to ascertain from the limited reporting of each of these events, but in at least several instances rescuers noted their feeling that using a combination of maneuvers simultaneously or sequentially had contributed to success. While it is hard to know from these reports whether in fact it was the combination of maneuvers in these cases that saved the victim, it is equally difficult to know whether techniques marked unsuccessful on some of the other reports did not in fact contribute to the ultimate success of the final maneuver, to which the success was solely attributed.

The latest clinical series has recently been reported by Dr. Edward Patrick.[23] In this report Dr. Patrick published a detailed questionnaire that, if correctly filled out, might help to clarify the sequence of events taking place in each individual rescue attempt. If accurately reported,

TABLE 4.—*Effectiveness of Food-Dislodging Maneuvers**

Maneuver	*Trials*	*Successes*	*Failures*
Back blows (BB)	109	53 (22)	56
Abdominal thrust (AT) ..	168	132 (74)	36
Chest thrust (CT)	25	16 (9)	9
Finger probe (FP	52	30 (9)	22
Instrumentation (IN) ...	18	13 (2)	5
Cardiopulmonary resuscitation (CPR) ...	14	12 (0)	2

Reported as "successful" when used as one or more maneuvers. Figures in parentheses indicate "successful" application with no other maneuver used.

*Reproduced with permission from Redding JS[22]; Copyright 1979, The Williams & Wilkins Co., Baltimore.

TABLE 5.—*Effectiveness of Subsequent Maneuvers After Initial Failures**

Initial Failures		*Successful Subsequent Maneuvers*
Back blows (BB)	56	AT 38, CT 4, FP 5, IN 4, AT+FP
Abdominal thrust (AT)	36	BB 14, CT 2, FP 5, IN 6, BB+CPR 2, IN+CPR
Chest thrust (CT)	9	BB 2, FP 2, IN 3, CPR
Finger probe (FP)	22	BB 4, AT 7, CT 2, IN 4, BB+CPR
Instrumentation (IN)	5	FP, BB+CPR
Cardiopulmonary resuscitation (CPR) ..	2	BB

Maneuvers or combinations of maneuvers reported as "successful" after reported "failure" with the initial measure applied.

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meticulous answering of the questionnaire should help to alleviate some of the confusion created in other clinical series. Nevertheless, it might still be difficult to ascertain whether sequential maneuvers have potentiating effects. In the same paper Dr. Patrick also reports his findings on 1,164 patients whose treatment outcome was evaluated. He then divides these 1,164 cases into two groups: Group I consists of 972 patients treated with the Heimlich maneuver alone or before other maneuvers; Group II is comprised of 192 patients who received back blows initially. Dr. Patrick presents a statistically significant increase in negative outcomes when the second group is compared with the first, and argues that current recommendations that the back blow be used first are dangerous.

There are a number of problems with Dr. Patrick's report. In the first place, less than 10 percent of the patients reported in this very large series actually filled out Dr. Patrick's questionnaire (personal communication). It is not clear how the data were gathered on the remaining 90 percent of the patients in the series. For this reason, there is a reasonable question as to the accuracy of the majority of these anecdotal reports.

In the second place, over 900 of the patients in the series represent testimonials gathered by and delivered to Dr. Patrick by Dr. Heimlich.

Third, negative outcome is defined in terms of the victim collapsing, becoming unconscious or dying. Onset of unconsciousness, or "collapsing," is more likely related to the degree of antecedent hypoxia at the time any given maneuver was introduced, rather than to the effect of that maneuver. Perhaps a more appropriate way to evaluate outcome would be to look at death or neurologic impairment following the event. This of course would be more difficult, but clearly very important. Dr. Patrick makes no attempt to evaluate neurologic outcome, and does not report incidences of death following back blows as compared to abdominal thrusts.

Finally, it is somewhat difficult to evaluate Dr. Patrick's choice of these two specific groups. If the more successful group consisted of patients who received the Heimlich maneuver *first* or alone, at least some members of this group must have had other maneuvers following the Heimlich maneuver, ostensibly because the Heimlich maneuver was unsuccessful by itself in removing the obstruction. It would be hard to use such cases to try to prove that these other maneuvers should not be used in the treatment of airway obstruction. It is not clear from Dr. Patrick's report what percentage of patients in this first group had the Heimlich maneuver alone, as compared to the Heimlich maneuver followed by other maneuvers. Evidently Dr. Patrick's data have been computerized, so it may be possible to retrieve numbers on a much larger and more detailed set of subgroups, including those who received only the Heimlich maneuver, or only back blows, and those who received several maneuvers in various combinations. Such information might be more helpful, but would still require careful evaluation because of the method of data collection.

Physiologic Data

There are to date four reports of experimental studies regarding the treatment of airway obstruction. In 1975 Dr. Heimlich measured the pressures generated, volume of air expelled and peak flow rates with the Heimlich maneuver in ten conscious human volunteers.[6] He also tested the Heimlich maneuver on four beagles who had been intubated with an endotracheal tube, the lumen of which had been plugged by a rubber stopper. After inflating the tubes' cuffs, Dr. Heimlich found that "the endotracheal tube (bolus) popped out of the trachea" in over 20 attempts, with no failures reported. Abdominal thrust during early expiration moved an average of 0.94 liter of air (0.35 liter was expelled when the maneuver was applied at end expiration) and peak flow rates of 205 liters per minute (74.9 liters per minute at end expiration) were measured.

In 1977 Dr. Charles Guildner and colleagues[24] reported a comparison of abdominal thrust and chest thrust in normal anesthetized human volunteers. They initially also attempted to measure the effects of back blows, but abandoned this because back blows were "so ineffective in creating air flow or increased pressure in the chest." Dr. Guildner and associates report significantly higher peak pressures, peak flows and vital capacities with the use of the chest thrust as compared with the abdominal thrust, in both the sitting and supine positions. They thus recommend the chest thrust as the procedure of choice, although inexplicably conclude the article by proposing a treatment regimen wherein back blows would be used before any thrust procedure.

Dr. Archer Gordon has completed the most extensive series of experiments on anesthetized apneic humans designed to evaluate artificial cough techniques.[14,25] He found first of all that none of

these procedures could generate comparable pressures, flows or volumes to that of normal cough. He also found that the effects of normal coughing are enhanced by increased precough volume in the lung, and noted that increased lung volume in turn increases the effectiveness of any of the artificial cough procedures.

Dr. Gordon also found that back blows produced substantially higher pressures and generated these pressures over a much shorter time than either chest thrust or abdominal thrust (see Figure 1). Chest thrust was found to be somewhere in between the other two. Chest thrust and abdominal thrust both produced higher volumes of air moved than the back blow, and the same was true for peak flows. Interestingly, external CPR produced results similar in all respects to those of chest thrusts and abdominal thrusts. None of these maneuvers approached the normal cough in effectiveness. Dr. Gordon speculates on the basis of

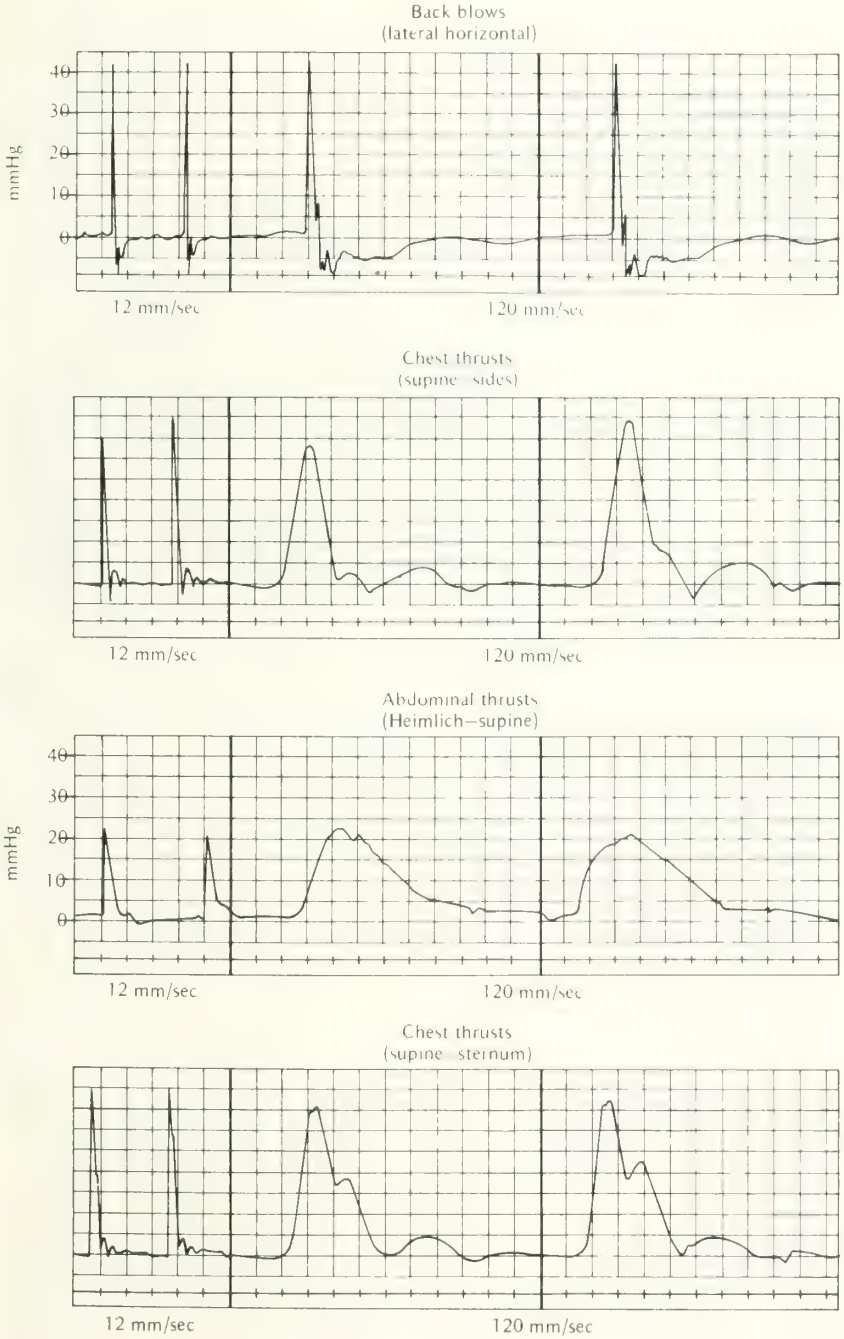

Figure 1.—Airway pressure during artificial coughs with airway blocked (humans). (Reproduced by permission from Gordon et al.[14])

his results that the instantaneous, rapid rises in intrathoracic pressure created by the back blow would be sufficient to disimpact foreign objects lodged at the level of the vocal cords, but would be insufficient to move such objects a great distance because of the small amount of air moved. Abdominal thrusts, on the other hand, along with chest thrusts, might on occasion deliver insufficient force to move objects impacted in the larynx (with high static resistance), but might move objects previously loosened by the back blow an appreciable distance in the posterior pharynx. He then suggests that a combination of these maneuvers, using the back blow first, should be superior to using any of the maneuvers alone. In a related study with both adult and infant baboons, he found that foreign bodies were in fact moved more successfully by a combination of maneuvers than by either back blows or abdominal thrusts alone.[25]

The final physiologic study comes from Dr. H. Ruben[15] of the University of Copenhagen. He used a silicone rubber cast of the human larynx, into which were placed various types of food pieces, to measure the amount of pressure necessary to move these foods. He subsequently measured pressures generated on both fresh cadavers and anesthetized humans following back blows, abdominal thrusts and chest thrusts. Finally, he attached the model larynx with the food fragments in place to the endotracheal tubes of intubated human subjects and analyzed the effectiveness of the various techniques.

Ruben found that the pressures required to remove food lodged in the model larynx varied with the type of food involved and with whether the food was wedged in an airtight manner or if an air leak was allowed. In general, pressures required to remove meat wedged in the larynx in an airtight position were far higher than those achieved with any of the artificial cough maneuvers. Partial obstructions, associated with air leaks, also required considerable pressures, though these were occasionally within the range of some of the maneuvers. Interestingly, ejection was easier if the model was inverted or if the pressure was applied in a series of jolts as opposed to steady pressure.

Ruben found that pressures generated by back blows were substantially higher than those generated by abdominal thrusts in both anesthetized human volunteers and fresh cadavers. Chest thrust also yielded higher pressure than did the Heimlich maneuver, although these pressures were slightly lower than those achieved with back blows. Rate of pressure rise was also greatest with back blows and least with abdominal thrusts (see Table 6 and Figure 2).

TABLE 6.—*Highest Recorded Intratracheal Pressure in 12 Anesthetized Human Volunteers**

	Heimlich Maneuver median (range) (cm H_2O)	*Sternal Thrust median (range) (cm H_2O)*	*Blow on Back median (range) (cm H_2O)*
Resting expiratory level	10 (4-20)	20 (6-22)	25 (12-30)
Inspiratory Volume 600 ml	16 (6-22)	30 (15-35)	32 (20-35)

*Reproduced by permission from Ruben & Macnaughton.[15]

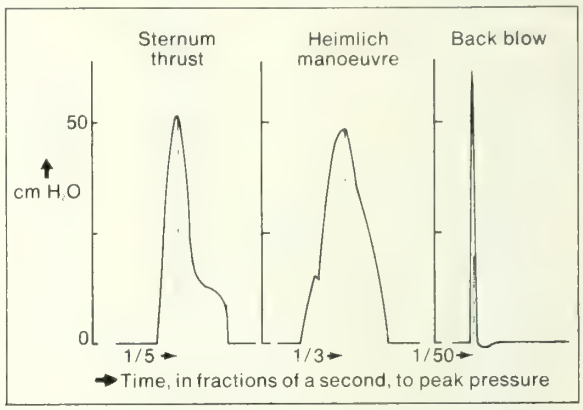

Figure 2.—Typical pressure waves recorded from chest thrust, Heimlich maneuver and back blow. (Reproduced by permission from Ruben & Macnaughton.[15])

When the model larynxes with the obstructing food were attached to the endotracheal tubes of intubated volunteers, successful removal was achieved only once, in a patient in whom an orange segment was attached to the model larynx, and only when the Heimlich maneuver in combination with the sternal thrust were aided by gravity.

Dr. Ruben concludes from his study that none of the maneuvers would be successful when a piece of meat is tightly wedged in a victim's larynx. With partial obstruction, back blows seem to be able to generate the type of rapid rise and total pressure necessary to move some types of food objects. Chest thrusts seem similarly able to do this, while abdominal thrusts generate considerably less pressure.

Dr. Ruben emphasizes the positive effects of gravity and the seeming importance of the rate of pressure rise in conjunction with the total pressure achieved. He further warns against finger

TABLE 7.—*Comparative Effects of Cough and Artificial Cough Maneuvers*

	Pressure (mm Hg)	*Volume (cc)*	*Flow (L/min)*
Cough			
Gordon et al[14]	72/115*	550/1,650*	198/378*
Back Blow			
Guildner et al[24] ...	..	...	...
Gordon et al[14]	25/45*	25	39
Ruben & Macnaughton[15] .	18/24*	...	...
Abdominal Thrust			
Heimlich et al[6] ...	31	940	205
Guildner et al[24] ...	19	380	65
Gordon et al[14]	11/15*	283	264
Ruben & Macnaughton[15] .	7/12*	...	...
Chest Thrust			
Guildner et al[24] ...	32	520	99
Gordon et al[14]	18/19*	240	276
Ruben & Macnaughton[15] .	15/22*	...	...

*Values of lung volume recorded at end inspiration.

probes in the posterior pharynx when unaided by direct visualization, as the possibility of even further wedging an object (however slightly) with digital pressure would seem to be associated with significantly greater difficulty in subsequently removing that object.

A comparison of the physiologic effects of each of the various maneuvers is made in Table 7. While the individual numbers generated seem to vary a great deal, it is reasonable to conclude that back blows produce higher and more rapid pressure rises than do the other maneuvers, while chest thrusts produce somewhat more substantial results than Heimlich maneuvers. Back blows produce the least effect in terms of flow rates and volume of air moved. Each of the maneuvers' effectiveness is enhanced when carried out at a higher lung volume, but none of the maneuvers approximates the effect of normal cough, particularly when cough is carried out at end inspiration.

Side Effects

General Considerations

Any of the maneuvers in question might be considered to have a deleterious effect on the basis of any or all of three possible mechanisms. The maneuvers may cause direct side effects, such as damage to vital organs. If they are ineffective, they may be deleterious by delaying other more effective maneuvers. Finally, they can directly and adversely affect the success of subsequent maneuvers by, for example, wedging the obstructing object even further into the larynx.

Back Blows

Back blows have been associated with a very low incidence of minor side effects, including sore ribs and back, and occasional nausea and vomiting after the maneuver.[21] Back blows take less than several seconds to perform, and thus should not influence the results of anoxia. We know that unconsciousness occurs early following global anoxia, from 8 to 12 seconds after its onset,[26] while irreversible neurological damage does not occur for at least 2 to 4 minutes, and death likewise does not occur for approximately 4 minutes or more.[27,28] Obviously there is no advantage in delaying adequate therapy for even a matter of several seconds, but the likelihood that this will substantially affect the final outcome is in fact very small.

Perhaps of greater concern is the possibility that back blows will wedge objects further in the larynx. This claim has been made by Dr. Heimlich,[10,29] who states that it has been substantiated by individual case reports, wherein children who were evidently choking on a piece of food but were able to move air and remain conscious, deteriorated following application of back blows. Several such anecdotal cases have been described by Dr. Heimlich. Dr. Heimlich also refers to the writings of Dr. Samuel Gross on this subject.[29] Dr. Gross, a nineteenth century American physician, collected several hundred cases of foreign body aspiration.[30] He described several cases wherein back blows contributed to total obstruction at the level of the larynx. He also warned against the use of back blows in breathing, conscious victims, and said that they should be reserved for a "last resort" effort.

Dr. Gross's observations and conclusions do not in fact in any way suggest that back blows move objects distally, thus driving them further into the larynx. Dr. Gross's case reports of back blows causing obstruction despite inversion of the victim were of children who aspirated small foreign objects not to the level of the larynx, but rather past the larynx and vocal cords and into the right mainstem bronchus. Such children then had cough and irritative pulmonary signs, but no signs of upper airway obstruction. In several cases zealous family members attempted to treat the problem by turning the child over and administering blows to the back, which occasionally caused the object to

move, not distally but proximally, down the trachea, where it was then wedged against the underside of the larynx. In several instances, this caused total obstruction of the upper airway and subsequent deterioration. This does not mean that back blows cause distal movement of foreign bodies, nor is it applicable to a discussion of upper airway obstruction. Anecdotal cases described by Dr. Heimlich where breathing and conscious children evidently deteriorated following back blows serve to emphasize the generally agreed upon point that patients with partial upper airway obstruction who are able to move adequate amounts of air should not in fact have any artificial cough techniques administered. These patients should be encouraged to take a deep breath and then cough. If this effort is unsuccessful in removing the object, the patient should be taken to a medical facility where instrumental removal of the foreign object can be done under direct visualization. Dr. Gross's recommendations that back blows be used only as a last resort, that is, in patients in whom airway obstruction is sufficient to occlude the airway and preclude adequate air movement, are still cogent today and hold true not only for back blows but also for all other artificial cough techniques. On the other hand, there is no theoretic or empiric reason to suspect that the back blow, which raises pressure in the thorax distal to the obstructing object, should cause any object to move retrograde and become more deeply wedged at the level of the vocal cords.

Abdominal Thrust

Dr. Heimlich notes that 11 cases of broken ribs secondary to abdominal thrust were reported in his first approximately 500 cases. He ascribes these to improper performance of the procedure. Other reported side effects include several instances of abdominal tenderness and nausea and vomiting; one case of retinal detachment; one case of a ruptured stomach and associated small laceration of the spleen with satisfactory outcome following surgical repair of the stomach and splenectomy, and one case of clinically insignificant pneumomediastinum.[21,31,32] Theoretic concerns have been raised about significant intra-abdominal organ damage and about the possibility of pulmonary aspiration, if and when the obstructing food bolus is cleared from the larynx following the forceful pressure delivered to an often full stomach by the Heimlich maneuver. Neither of these potential complications has been reported, nor have any other major adverse effects. It is worth noting that the Heimlich maneuver might well take considerably longer to perform than back blows.

Chest Thrust

Experience with the chest thrust is much more limited than with either the Heimlich maneuver or back blows. No substantial side effects have been reported, although chest soreness following chest thrust was reported in the American Heart Association series.[21] Concern has been raised about the possibility of not only broken ribs and sternal fractures, but of any and all of the side effects noted during external CPR. These include myocardial contusions, pneumothoraces and intra-abdominal organ damage, among others.[13] On the basis of these proposed potential complications, Dr. Heimlich and others have suggested that the chest thrust is too dangerous to use routinely. While a number of noteworthy complications have in fact been reported with external CPR, they have occurred following many thousands of applications of external CPR. Not only has external cardiac massage been done on an extremely large number of patients (a group many times the size of the group that has received any of the artificial cough maneuvers), but multiple external compressions are done during each single resuscitation. Thus the true incidence of side effects with external CPR is extremely small and may not in fact exceed that of any of the external cough maneuvers. It is difficult, therefore, to exclude chest thrust from our therapeutic armamentarium for the treatment of upper airway obstruction on the basis of assumed similarity to another procedure that is, from all we know, extremely safe.

Finger Probe

Attempts to manually extract foreign bodies from the back of the throat have not been discussed in detail in this paper. These attempts, whether with the rescuer's fingers or with some form of instrument, are the method of choice when there is direct visualization of the object. However, in the absence of visualization, these methods, though moderately successful according to clinical reports,[21] seem to be quite dangerous.[15] Not only have they caused minor side effects such as loose teeth and pharyngeal abrasions,[21] but there is a substantial risk of further impaction of the foreign body, with resultant inability to remove it by any of the artificial cough techniques. Drs. Ruben and Macnaughton's study indicates

that slightly increased wedging of an object into the larynx requires greatly increased pressures to remove that object.

Artificial Cough Techniques—Summary

Back Blows

At this point, all available evidence suggests that the back blow is an easily and rapidly executed maneuver that seems to have moderate clinical success. It increases intrathoracic pressures, which should result in effectively removing tightly wedged foreign bodies from the larynx. Back blows should be followed by other maneuvers, such as the abdominal thrust or chest thrust, to move the object out of the larynx. While there has been speculation about possible adverse effects of this maneuver, there is no evidence at this point that the procedure carries any major risk.

Abdominal Thrust

The abdominal thrust, or Heimlich maneuver, is associated with a large number of documented clinical successes. While we should be somewhat cautious about interpreting these anecdotally reported successes, the Heimlich maneuver has a strong place in the treatment of upper airway obstruction. Nevertheless, experimental studies showing that it is incapable of substantially increasing intrathoracic pressures, and that it is particularly incapable of producing a rapid rise in pressure, suggest that its success will be greatest if it follows another maneuver, such as back blow, that might loosen or dislodge a wedged object. While there are potential complications to the Heimlich maneuver, current experience indicates that it is a fairly safe procedure.

Chest Thrust

There are fewer anecdotal data regarding the clinical effectiveness of the chest thrust, though in terms of percentages of success, it is roughly as successful as the Heimlich maneuver. Experimental evidence demonstrates that the chest thrust produces higher intrathoracic pressure than does the abdominal thrust and, in the absence of any hard evidence that the chest thrust is associated with notable morbidity, it may well be preferable to the abdominal thrust. At this point, however, we probably do not have enough data to clearly recommend one of these maneuvers over the other.

Finger Probe

While the finger-probe technique, along with other attempts at directly removing an obstructing object, has had some success clinically, in light of its potential for worsening the situation, it probably should be employed only under direct visualization or as an absolutely last resort.

Conclusions and Recommendations

There has been much sound and fury regarding the appropriate treatment of foreign body obstruction of the upper airway, but there is a paucity of hard data. The limited clinical data that we do have are retrospective, anecdotal and testimonial and, for the most part, poorly reported by lay rescuers. The data suggest mixed results with reasonably high success with thrust techniques. They also suggest that a combination of maneuvers is superior to any single maneuver.

Most attempts at treating foreign body upper airway obstruction are performed not in the setting of a professional office or hospital environment, but rather by civilians in public places such as restaurants. Thus, our energy should be directed to appropriately teaching the lay public how to treat upper airway obstruction. We have learned in our attempts to teach CPR that there is a tremendous and rapid attenuation of skills following complex courses for citizens.[33-36] Citizen CPR providers are able to remember cognitive details such as how to recognize cardiac arrest, but rapidly lose their ability to remember exact performance details, such as compression and ventilation rates and ratios. It seems unreasonable, therefore, to ask the public to memorize complicated treatment sequences for the management of upper airway obstruction, such as those presently suggested by the American Red Cross and the American Heart Association. Rather, it might be more effective to teach the public a limited number of important facts about the subject. We should stress the recognition of upper airway obstruction and a variety of techniques for dealing with it, such as the back blow (which is obvious and very easy to learn) and one of the thrust techniques, as well as external CPR.

We should encourage people to refrain from doing any of these maneuvers if the victim is breathing and spontaneously able to cough. We should suggest that they do each of these maneuvers in whatever sequence they can remember, and with successive repetitions, when they are confronted with a patient with a totally obstructed airway, while simultaneously contacting their emergency medical service system. Repeated attempts should be continued until professional

help arrives, as initial failure may be reversed when laryngospasm abates with the onset of coma. Nevertheless, some cases may require direct laryngoscopic visualization and instrumental removal of the foreign body.

REFERENCES

1. Heimlich HJ: Pop goes the cafe coronary. Emergency Med 6:154-155, 1974

2. Haugen RK: The cafe coronary: Sudden death in restaurants. JAMA 186:142-143, 1963

3. National Academy of Sciences, National Research Council: Cardiopulmonary resuscitation. JAMA 198:372-379, 1966

4. Eller WC, Haugen RK: Current concepts: Food asphyxiation —Restaurant rescue. N Engl J Med 289:81-82, Jul 12, 1973

5. Heimlich HJ: A life-saving maneuver to prevent food choking. JAMA 234:398-401, 1975

6. Heimlich HJ, Hoffman KA, Canestri FR: Food-choking and drowning deaths prevented by external subdiaphragmatic compression—Physiological basis. Ann Thorac Surg 20:188-195, Aug 1975

7. Committee on Emergency Medical Services, Assembly of Life Sciences: Report on Emergency Airway Management. National Research Council, National Academy of Sciences, 1976

8. Heimlich HJ: Back blows or death blows. Emerg Med Srvs 8:88-95, 1979

9. Heimlich HJ: The Heimlich maneuver versus back blows for choking victims. Emerg Med Srvs 9:11-37, 1980

10. Heimlich HJ: Controversial panel on the Heimlich maneuver. American College of Emergency Physicians Scientific Assembly, Las Vegas, Nevada, 1980

11. Statistical abstracts of the U.S.—1978, ed 99. United States Dept of Commerce, Bureau of Census, 1978, p 75

12. Accident Facts. National Safety Council, Chicago, 1977

13. Standards and Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC): Part II.—Adult basic life support. JAMA 244:460-471, Aug 1, 1980

14. Gordon AS, Belton MK, Ridolpho PF: Emergency management of foreign body obstruction, chap 6, Safar P (Ed): Advances in Cardiopulmonary Resuscitation. New York, Springer-Verlag, 1977

15. Ruben H, Macnaughton FI: The treatment of food-choking. Practitioner 221:725-729, Nov 1978

16. Patrick EA: Controversial panel on the Heimlich maneuver. Presented at the American College of Emergency Physicians Scientific Assembly, Las Vegas, Nevada, 1980

17. Standards for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC). JAMA 227(Suppl):837, 1974

18. Cullen W: A letter to Lord Cathcart concerning the recovery of persons drowned and seemingly dead. Edinburgh, William Creech, 1791

19. Ramsey D: A review of the improvement and state of medicine in the XVIIIth century. Charleston, WP Young, 1801

20. Hughes T: Comparative analysis of Dr. Henry J. Heimlich's data on 536 case reports of the application of the Heimlich maneuver. Submitted to National Research Council, July, 1976

21. American Heart Association Subcommittee on Emergency Cardiac Care: Reaffirmation of the American Heart Association's Position on the Emergency Treatment of the Obstructed Airway. American Heart Association document COM/SI 80-511B, Jan 1979

22. Redding JS: The choking controversy: Critique of evidence on the Heimlich maneuver. Crit Care Med 7:475-479, 1979

23. Patrick EA: Choking—A questionnaire to find the most effective treatment. Emerg Med Srvs 9:59-64, 1980

24. Guildner C, Williams D, Subitch T: Airway obstructed by foreign material: The Heimlich maneuver. JACEP 5:675-677, 1977

25. Gordon AS: Emergency airway management. Presented at the 3rd annual UCLA School of Medicine Postgraduate Institute on Emergency Medicine, 1978

26. Rossen R, Kabat H, Anderson JP: Acute arrest of cerebral circulation in man. Arch Neur Psych 50:510-528, 1943

27. Cole SL, Corday E: Four minute limit for cardiac resuscitation. JAMA 161:1454, 1956

28. Lund I, Skullberg A: Cardiopulmonary resuscitation by lay people. Lancet 2:7988, 1976

29. Heimlich HJ, Uhley MH: The Heimlich maneuver. Clin Symp 31:3-34, 1979

30. Gross SK: A Practical Treatise on Foreign Bodies in the Air Passages. Philadelphia, Blanchard and Lea, 1854

31. Visintine RE, Baick CH: Ruptured stomach after Heimlich maneuver. JAMA 234:415, Oct 27, 1975

32. Agia GA, Hurst DJ: Pneumomediastinum following the Heimlich maneuver. JACEP 8:473-475, Nov 1979

33. Weaver FJ, Ramirez AG, Dorfman FB, et al: Trainees' retention of cardiopulmonary resuscitation: How quickly they forget. JAMA 241:901, 1979

34. Alvarez H III, Cobb L: Experiences with CPR training of the general public, *In* Proceedings of the National Conference on Standards for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC). Dallas, American Heart Association and National Academy of Sciences, National Research Council, 1975, p 33

35. Banasik Z, Sledzinski Z, Arciszewski B, et al: The usefulness of Resusci-Anne mannequin in teaching modern methods of resuscitation. Anaesth Resusc Intensive Ther 4:131-137, 1976

36. Vanderschmidt H, Burnap T, Thwaites J: Evaluation of cardiopulmonary resuscitation course for secondary schools. Med Care 13:763, 1975

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Medical Progress

Advances in Plastic Surgery

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Recent progress in plastic surgery has been rapid and many new techniques have been developed. Reconstructive procedures have been advanced by a better understanding of the anatomy of the blood supply to skin and muscle, with the subsequent development of the use of axial flaps, musculocutaneous flaps and neurosensory flaps. Burn treatment has advanced greatly, making it possible to successfully treat larger and more complicated burns. The development of microsurgery has made possible free-flap transfer and replantation of amputated parts. Advances in surgical procedures on the hands include a realization that primary repair of lacerated tendons and nerves will give good results. Replacement joints have been developed that can be used in hands for joints destroyed by arthritis or trauma. Craniofacial surgery is a new field of endeavor in plastic surgery, involving new techniques that can be used to treat exophthalmos of Graves' disease and the facial deformities resulting from gigantism and acromegaly. Head and neck procedures have advanced, with the emphasis on immediate reconstruction using new flaps. Techniques for treating cleft lip and palate have been refined. Encouraging results have been reported in the treatment of nevus flammeus with argon lasers. In aesthetic surgical procedures, the aim is for safety and consistent long-lasting results. Improved understanding of the physiology and treatment of radionecrosis has evolved.

PLASTIC SURGERY is the use of surgical procedures to achieve appearance and function that is as near to normal as possible. The areas of interest of plastic surgeons include congenital anomalies such as facial clefts, craniofacial dysostosis, microtia, extensive nevi, hemangiomas, congenital bands and cysts, and syndactylism. Treatment of traumatic defects; malignant conditions of the extremities, neck and trunk; facial fractures, and burns, as well as aesthetic surgery, are all parts of a plastic surgeon's concern. The purpose of this article is to identify some of the recent advances in plastic surgery, discuss them and point out their usefulness in treating some of the problems physicians encounter.

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Reconstructive Plastic Surgery

Extensive study of the minute anatomy of the blood supply of tissues in the body has resulted in recent discoveries that enable us to transfer blocks of tissue—procedures that heretofore would not have been possible. The basis for trans-

fer of tissue in the classical sense in plastic surgery was the random-pattern flap. The amount of tissue that could be safely moved at any one time was limited by the blood supply to the tissue; it was known that this could be increased by depriving the tissue of some of its blood supply or delaying the transfer of the tissue. The use of flaps to reconstruct defects was somewhat complicated by the fact that in some cases multiple operative procedures were required to "migrate" the tissue to the designated area. Daniel and Williams[1] pointed out the importance of the skin's blood supply in the planning of a skin flap. They noted that the earlier method of flaps was based on the assurance of a blood supply that came through the underlying muscle tissue by a perforator artery to supply the dermal-subdermal plexus and thereby the skin. This was the basis of the random-pattern flap.

Daniel and Williams also pointed out that in some areas of the body there is a direct blood supply to the skin through a cutaneous artery. Flaps based on a direct artery are called axial-pattern flaps. It was noted that it is not necessary to delay these flaps in order to transfer a relatively large amount of tissue along the long axis of the supplying vessel. Two examples of this type of flap are the deltopectoral flap, described by Bakamjian,[2] and the groin flap, described by McGregor and Jackson.[3]

Vasconez and colleagues,[4-6] McGraw,[4-9] Mathes[5,6] and others have contributed to the rapid advancement of knowledge about the blood supply of individual muscles and its usefulness in reconstruction. The awareness that there is a vascular dominance to muscles in the body, and that skin could be transferred intact with underlying muscle contributed substantially to the development of the new myocutaneous flaps, which have revolutionized reconstructive plastic surgery. We can now transfer in one stage large amounts of skin, or skin and muscle, or skin, muscle and bone in the local area of the donor, or these tissues can be transferred to remote sites away from the donor area by dissecting them free on their vascular pedicle and transferring them as microvascular free flaps.

Breast Reconstruction

New and more satisfactory techniques for reconstruction of breasts following mastectomy have evolved rapidly over the recent past. Using knowledge of the blood supply to skin and muscle, it is possible to reconstruct a breast in most cases of mastectomy regardless of how radical the surgical removal was. The use of a thoracoepigastric flap[10] from the epigastric area to the chest area can provide tissue to reconstruct a breast mound. If a large amount of tissue was removed by the surgical procedure we can transfer tissue from the back by moving the latissimus dorsi muscle[11] with overlying skin to the anterior chest and effect a satisfactory and safe coverage for a prosthesis. In classical radical mastectomy where the clavicular head of the pectoralis muscle has been excised, one can move the insertion of the latissimus dorsi from the posterior aspect of the humerus around to the stump of the pectoralis major muscle on the anterior aspect of the humerus, thereby eliminating the postsurgical hollow.

After an adequate breast mound has been reconstructed one can reconstruct the nipple areola complex using a variety of tissues. In the usual reconstructive procedure the pigmented skin on the medial aspect of the upper thigh is used for the areola,[12] sharing a portion of either the opposite nipple or an ear lobe[13] to reconstruct the nipple.

Pressure Sores

Treatment of pressure sores has been aided by new knowledge and techniques in plastic surgery. Dibbell[14] showed that it is possible to move innervated tissue to denervated areas of the body and thereby provide protective sensation to neurologically impaired persons such as paraplegic and meningomyelocele patients. Using this technique it is possible to give a neurologically impaired patient the ability to sense pressure and thereby prevent recurrent pressure ulcers. The mainstay of treatment of these decubitus ulcers continues to be prevention but, with the use of innervated flaps, muscle[15] and muscle-skin[16,17] flaps for additional padding with a good blood supply, it is possible to care for these patients in a more satisfactory way.

Burns

The management of burns has been considerably improved by new techniques. Immediate cooling of the area of burn has been shown to have a beneficial effect on the microcirculation.[18] It has been discovered that the condition of a badly burned patient in shock can be greatly improved by the rapid and immediate infusion of fluids to prevent the complications of burn shock.[19] With

the ability to get the patient through the initial burn shock, the next problem encountered is that of burn-wound sepsis. Our ability to handle burn-wound sepsis has been greatly enhanced by the development of new topical antibiotics. Historically, silver nitrate solution was an effective topical antibacterial agent; however, it had certain disadvantages, one being that it stained everything with which it came in contact. Other agents needed to be developed. As a result mafenide acetate (Sulfamylon), silver sulfadiazine (Silvadene) and povidone-iodine (Betadine) have emerged as effective topical antibacterial agents. The use of biological dressings such as allografts (also called homografts) and pigskin xenografts (heterografts) has enhanced our ability to conserve the patients' fluids and keep them comfortable during burn treatment. Tangential excision[20] and enzymatic debriding agents have been developed that aid in the rapid debridement of the burn wound in preparation for grafting. Sutilains ointment (Travase)[21] is one of the agents that has been used successfully.

There is a growing realization that pulmonary injury substantially complicates the extent of trauma and the treatment of a burn.[22] Many people who are subjected to fires die from the pulmonary injury before they reach the hospital. Usually there is direct injury of the tracheobronchial tree from the poisonous components of the smoke inhaled at the site of the fire. Recognition and early treatment of pulmonary injuries has saved many patients' lives.

Hyperalimentation has helped burn patients survive the massive demands for calories brought on by the burn.[23] Advances have been made in the rehabilitation of postburn patients by the early use of splinting and range-of-motion exercises during the treatment of the burn. The early post-grafting application of pressure garments has helped to control the amount of scarring that may result from a burn.[24]

Microsurgery

Microsurgical techniques were developed in the laboratory by such pioneers as Buncke.[25,26] The development of microsurgery into a clinical tool in plastic surgery was made possible by advances in the manufacture of optics, fine instruments and fine sutures that made them readily available. Using microsurgical techniques it is now possible to move large blocks of tissue from one location of the body to another in one operation, making it feasible to more easily reconstruct damaged parts of the body. For example, it is now possible to move a toe to the hand to make a new thumb.[27] Skin with its cutaneous nerve can be moved from one area to another and a microvascular and microneural repair carried out, thus establishing coverage with protective sensation.[28] Microvascular free flaps of skin,[29] skin and muscle,[30] and of skin and bone[31] are now possible. Using microsurgical techniques it is now possible to reimplant amputated parts such as fingers, hands[32] and other parts of the body with a very high degree of success. Results are better in clean amputations and decrease as the amount of crush and avulsion increase. The amputated part should be placed in saline in a plastic bag and placed on ice for transport to a replant center.

Hand Surgery

A new consensus on the primary repair of lacerated flexor tendons is emerging. Kleinert[33] and Verdan[34] feel that if a flexor tendon is lacerated in the area between the distal palmar crease and the proximal interphalangeal joint, and the wound is clean, the tendons should be repaired primarily. Their results using primary repair of flexor tendons have been good. It is important, however, that the repair be carried out by a surgeon experienced in surgical procedures on the hand.

Primary repair of lacerated peripheral nerves in the upper extremity has yielded improved results through the use of magnification, fine instruments and fine sutures, making possible very accurate anatomic approximation of the lacerated nerve.[35] In a sharp laceration involving the nerve, most surgeons now feel that the earlier and the more accurate the repair, the better the eventual outcome.[36] Treatment of fractures of the small bones of the hand has been improved by the use of the small fragment fixation set developed in Switzerland.[37] Using this technique it is possible to get very accurate reduction and rigid fixation of the fracture resulting in less deformity and better function following treatment of the fracture than has been the case in the past.

The team approach is very helpful in the treatment of rheumatoid arthritis. A team consisting of a physician, a hand surgeon, an orthopedic surgeon and a therapist seems to offer the patient the best opportunity for treatment of this disease. Early synovectomy with balancing operations have been helpful in treating a patient with rheumatoid

arthritis of the hand.[38] In advanced cases, silastic-implant arthroplasties have been helpful in restoring function.[39] Silastic joint implants may also be useful in joints destroyed by trauma. The emergence of specialized hand therapists has helped improve the outcome of most hand problems.

Craniofacial Surgery

Craniofacial surgery is one of the dynamic new surgical disciplines in the field of plastic surgery. Dr. Paul Tessier[40] of Paris found that one could safely free the soft tissue off the underlying craniofacial skeleton, and move the bones freely. This included moving both orbits. By combining the techniques of plastic and neurosurgery, he showed that one could correct the deformities of the cranium, the orbit and the face in one stage. Craniofacial surgical techniques have been used to correct hypertelorism,[41] the increased distance between the orbits, by moving the orbits closer together without interfering with vision.

These techniques have also been used to correct the craniofacial deformities of Apert's and Crouzon's diseases,[42] which consist of synostosis of the coronal suture and at times other sutures of the skull. The synostosis results in a flattened forehead, bulging eyes and a retrusive midface. The trend is increasingly toward surgical intervention early in life to help prevent the sequelae of cranial stenosis and make it possible for patients afflicted with this condition to have a relatively normal appearance as children. Hoffman[43] developed a new technique in releasing cranial stenosis in which he advances a rim of supraorbital bone to allow the frontal lobe to move forward, releasing the trapped brain for normal growth. The craniofacial approaches that were developed initially by Tessier and advanced by others have been successfully used in the correction of the severe deformities seen in craniofacial fractures[44] and in the treatment of craniofacial tumors. The exophthalmos of Graves' disease can be successfully treated using these techniques to expand the orbit.[45] The facial deformities seen with gigantism and acromegaly can also be treated using these newer surgical techniques.

Head and Neck Surgery

The use of computerized tomography has improved the ability to evaluate the extent of tumors in the head and neck area, thereby enabling physicians to more accurately plan the treatment of the tumor. A close working relationship has developed among surgeons, chemotherapists and radiation therapists in the treatment of malignant conditions of the head and neck. It is generally accepted that in patients with tumors of moderate to advanced severity the survival rate is enhanced by the use of surgical procedures combined with radiation or chemotherapy (or both). Immediate reconstruction in head and neck cancer patients has been improved by the development of new techniques for using muscle and musculocutaneous flaps around the neck and upper thorax. These flaps are very helpful in covering surgical defects or in treating complications of radiation therapy. The most effective flaps for use in the treatment of defects in this area are the pectoralis major,[46] trapezius,[47] sternomastoid[48] and latissimus dorsi[49] flaps. The muscle can be based on its individual artery, and can be used to carry skin or skin and bone with it. The use of these newer flaps has reduced the period of disability, the discomfort and the length of hospital stay for patients by making it possible to carry out the reconstruction in one stage.

Congenital Defects

Cleft Lip and Cleft Palate

The treatment of cleft lip and cleft palate was considerably advanced by the realization that the muscles in both a cleft lip[50,51] and cleft palate[52] are abnormally inserted and that by freeing them from their abnormal insertion and joining them in a normal way, a much more functional and aesthetic result can be achieved from the repair. It has been noted that 90 percent to 100 percent of infants with cleft palate will have fluid behind the eardrum, so that it is important to have an otologist on the team when treating patients with cleft palates. The insertion of tubes or buttons in the eardrum, when necessary, has substantially reduced the incidence of permanent hearing loss in patients with cleft palates.[53] Bone grafting of the cleft palate early in the child's life has been shown to interfere with growth of the midface, and there is now a trend to postpone this procedure until a later age.[54] We have also noted an improvement in the methods of correction of late deformities of cleft palates and lips, notably facial bone osteotomies to improve facial symmetry and dental occlusion.

Vascular Lesions

The realization that many of the hemangiomas present in childhood will regress and almost com-

pletely disappear by the age of six has greatly improved the long-term results in these lesions.[55] Once the diagnosis of involuting hemangioma has been made, the most important treatment is that of reassurance to the parents that patience is the best course.

Treatment of a port-wine stain, or nevus flammeus, with argon laser has shown some encouraging results.[56] Laser treatment substantially lightens the color of the lesion in about 60 percent to 70 percent of patients, and may flatten the cobblestone texture noted in these lesions in adulthood. Treatment has been more successful in head and neck lesions than in trunk and extremity ones. As with all modes of treatment some difficulties have been noted, particularly scarring and especially scarring in the area around the mouth.

Aesthetic Surgery

The emerging philosophy in aesthetic surgery is to aim for safety—that is, to obtain the best possible results with a minimum of risk to the patient and with minimal scarring as a result of operation. Recently plastic surgeons have been striving for longer lasting results in facelift surgery by manipulating the platysma muscle and the superficial musculoaponeurotic layer.[57] The trend in rhinoplasty procedures is to do less but with meticulous attention to detail, attempting to balance the appearance of the nose with the face of the patient.[58]

Breast reduction in women with very large breasts results in some of the happiest patients seen by plastic surgeons. The surgical reduction of the weight of the breast can dramatically reduce the discomfort in the upper back and shoulders suffered by some of these patients for years. The trend in augmentation mammoplasty is to improve the safety and long-term results of the operation. Innovations in this operation include the development of improved prosthetic implants, and placement of the implant beneath the pectoralis major muscle in selected patients.

"Radionecrotic Ulcers"

With increasing therapeutic use of radiation therapy, a number of patients are seen with hypoxic ulcers caused by the irradiation. If the ulceration involves the underlying bone, an even more challenging wound occurs—an osteoradionecrosis.

The basic pathological feature of these ulcerations is a considerable decrease in the blood supply to the tissues, resulting in relative cellular hypoxia. This decrease in blood supply is the direct result of irradiation on the blood vessel wall and of fibrosis of the surrounding tissues.

The lumen of the blood vessels decreases in diameter due to thickening of the arterial wall caused by proliferation of the intima and hypertrophy of the media. There is also an extrinsic pressure on the blood vessel wall from fibrosis of the surrounding tissue, which further narrows the lumen. A relatively minor trauma will then result in an ulceration that is very prone to infection from surface bacteria, and the result is a self-perpetuating ulcer. The treatment of anoxic radiation ulcers consists of meticulous asepsis and the use of topical antibacterials, such as silver sulfadiazine or povidone-iodine. If the ulceration is small, it may heal over a relatively long time. Skin grafts are only rarely successful.

For large established postradiation ulcers, the treatment advocated by Blair and Brown in 1948 consists of total excision of the ulceration, including the surrounding irradiated tissue beyond the area of the telangiectasia. The rather large defect is then covered with tissue that brings in its own blood supply. This is best done by the transfer of myocutaneous omental flaps. Muscle in particular brings in a considerable volume of new blood to this relatively hypoxic area.

This principle is applied to the treatment of patients with osteoradionecrosis of the mandible. It is now possible to cover the exposed mandible, avoiding mandibulectomy, with the pectoralis or trapezius musculocutaneous flap. The wound usually heals and the patient is relieved of the pain and misery associated with this condition.

In the chest, painful ulcers over the sternum, clavicle and axilla resulting from radiation therapy for carcinoma of the breast are excised, including the underlying bones and ribs. The chest cage is stabilized by using polypropylene mesh, which is then covered with omentum and skin graft. Omentum is another tissue that is quite malleable and contains an abundant blood supply. Smaller defects over the chest, shoulder and axilla may also be covered by a latissimus dorsi myocutaneous flap.

Radiation ulcers over the pubis resulting from therapy for carcinoma of the cervix can be excised and the defect covered with the rectus or the tensor fascia lata musculocutaneous flap. These ulcera-

tions that in the past were almost untreatable can now be handled with considerable ease.

Agonizing sacral ulcers from external radiation treatment for carcinoma of the prostate or cervix can now be successfully treated by excision and coverage with the superior half of the gluteus maximus myocutaneous flap from one or both sides.

This principle is applicable anywhere in the body where a postradiation ulcer due to anoxia is excised and the defect is covered by muscle alone, omentum or a musculocutaneous flap.

REFERENCES

1. Daniel RK, Williams HB: The free transfer of skin flaps of microvascular anastomosis. Plast Reconstr Surg 52:16-31, 1973

2. Bakamjian VY: A technique for primary reconstruction of the palate after radical maxillectomy for cancer. Plast Reconstr Surg 31:103-117, 1963

3. McGregor IA, Jackson IT: The groin flap. Brit J Plast Surg 25:3-16, 1972

4. Vasconez L, Bostwick J III, McGraw JB: Coverage of exposed bone by muscle transposition and skin grafting. Plast Reconstr Surg 53:526-530, 1974

5. Mathes S, McGraw JB, Vasconez L: Muscle transposition flaps for coverage of lower extremity defects: Anatomic considerations. Surg Clin North Am 54:1337-1354, 1974

6. Mathes S, Vasconez L, Jurkiewicz MJ: Extensions and further applications of muscle flap transposition. Plast Reconstr Surg 60:6-13, 1977

7. McGraw JB, Massey FM, Shanklin KD, et al: Vaginal reconstruction with gracilis myocutaneous flaps. Plast Reconstr Surg 58:176-183, 1976

8. McGraw JB, Dibbell DG: Experimental definition of independent myocutaneous vascular territories. Plast Reconstr Surg 60:212-220, 1977

9. McGraw JB, Dibbell DG, Carroway JH: Clinical definition of independent myocutaneous vascular territories. Plast Reconstr Surg 60:341-352, 1977

10. Cronin TD, Upton J, McDonough JM: Reconstruction of the breast after mastectomy. Plast Reconstr Surg 59:1-14, 1977

11. Bostwick J III, Vasconez L, Jurkiewicz MJ: Breast reconstruction after radical mastectomy. Plast Reconstr Surg 61:682-693, 1978

12. Broadbent TR, Woolf RH, Metz PS: Restoring the mammary areola by a skin graft from the upper inner thigh. Brit J Plast Surg 30:220-222, 1977

13. Brent B, Bostwick J III: Nipple-areola reconstruction with auricular tissues. Plast Reconstr Surg 60:353-361, 1977

14. Dibbell DG: Use of a long island flap to bring sensation to the sacral area in young paraplegics. Plast Reconstr Surg 54:220-223, 1974

15. Ger R: The surgical management of decubitus ulcers by muscle transposition. Surgery 69:106-110, 1971

16. Minami RT, Mills R, Pardoe, R: Gluteus maximus myocutaneous flaps for repair of pressure sores. Plast Reconstr Surg 60:242-249, 1977

17. Minami RT, Hertz VR, Vistnes LM: Use of vastus lateralis muscle flap for repair of trochanteric pressure sores. Plast Reconstr Surg 60:364-368, 1977

18. DeCamera-Robson ML: Plastic surgical forum. Presented at the annual meeting of the American Society of Plastic and Reconstructive Surgeons, New Orleans, 1980

19. Baxter CR: Crystalloid resuscitation of burn shock, *In* Stone H, Polk HA (Eds): Contemporary Burn Management. Boston, Little Brown and Company, 1971, pp 7-32

20. Janzekovic A: A new concept in the early excision and grafting of burns. J Trauma 10:1103-1108, 1970

21. Pennisi VR, Capozzi A, Friedman G: Travase, an effective enzyme for burn debridement. Plast Reconstr Surg 51:371-376, Apr 1973

22. Achauer BM, Allyn PA, Furnas DW, et al: Pulmonary complications of burns: The major threat to the burned patient. Ann Surg 177:311-319, 1973

23. Wilmore DW: Nutrition and metabolism following thermal injury. Clin Plast Surg 1:603-619, 1974

24. Larson DL, Abston S, Evans EB, et al: Techniques for decreasing scar formation in the burned patient. J Trauma 11: 807-823, 1971

25. Buncke HJ Jr, Schulz WP: Total ear reimplantation in the rabbit utilising microminiature vascular anastomoses. Brit J Plast Surg 19:15-22, 1966

26. Buncke HJ Jr, Buncke CM, Schulz WP: Immediate Nicoladoni procedure in the Rhesus monkey, or hallux-to-hand transplantation, utilising microminiature vascular anastomoses. Brit J Plast Surg 19:332-337, Oct 1966

27. Cobbett JR: Free digital transfer: Report of a case of transfer of a great toe to replace an amputated thumb. J Bone Joint Surg [Br] 51:677-679, 1969

28. Daniel RK, Terzis J, Medgley RD: Restoration of sensation to the anesthetic hand by free neurovascular flap from the foot. Plast Reconstr Surg 57:275-280, 1976

29. Daniel RK, Taylor GI: Distant transfer of an island flap by microvascular anastomoses. Plast Reconstr Surg 52:111-117, 1973

30. Maxwell GP, Stueber K, Hoopes JE: A free latissimus dorsi myocutaneous flap. Plast Reconstr Surg 62:462-466, 1978

31. Buncke HJ Jr, Furnas DW, Gordon L, et al: Free osteocutaneous flap from a rib to the tibia. Plast Reconstr Surg 59: 799-811, 1977

32. Kleinert HE, Serafin D, Kutz JE, et al: Reimplantation of amputated digits and hands. Orthop Clin North Am 4:957-967, Oct 1973

33. Kleinert HE, Kutz JE, Atasoy E, et al: Primary repair of flexor tendons. Orthop Clin North Am 4:865-876, Oct 1973

34. Verdan CE: Primary and secondary repair of flexor and extensor tendon injuries, *In* Flynn JE (Ed): Hand Surgery, 2nd Ed. Baltimore, Williams and Wilkins, 1975, pp 144-176

35. Smith JW: Microsurgery of peripheral nerves. Plast Reconstr Surg 33:317-329, 1964

36. Grabb WC: Median and ulnar nerve suture—Experimental study comparing primary and secondary repair in monkeys. J Bone Joint Surg [Am] 50:964-972, 1978

37. Heim U, Pfeiffer KM: Small Fragment Set Manual. New York, Springer-Verlag, 1974

38. Barron JN: Assessment of suitability for surgery in general timing of operation. Ann Rheum Dis 28:74-76, 1969

39. Swanson AB: Flexible implant arthroplasty for arthritic finger joints: Rationale, technique, and results of treatment. J Bone Joint Surg [Am] 54A:435-455, Apr 1972

40: Tessier P: Relationship of craniostenoses to craniofacial dysostoses, and to faciostenoses: A study with therapeutic implications. Plast Reconstr Surg 48:224-237, Sep 1971

41. Tessier P, Guiot G, Derome P: Orbital hypertelorism: Definite treatment of orbital hypertelorism by craniofacial or by extracranial osteotomies. Scand J Plast Reconstr Surg 7:39-58, 1973

42. Tessier P: The definitive plastic surgical treatment of the severe facial deformities of craniofacial dysostosis. Plast Reconstr Surg 48:419-442, Nov 1971

43. Hoffman HJ, Mohr G: Lateral canthal advancement of the supraorbital margin. J Neurosurg 45:376-381, 1976

44. Tessier P: Total osteotomy of the middle third of the face for faciostenosis or for sequelae of LeFort III fractures. Plast Reconstr Surg 48:533-541, 1971

45. Wolfe SA: Modified three-wall orbital expansion to correct persistent exophthalmos or exorbitism. Plast Reconstr Surg 64: 448-455, 1979

46. Ariyan S: The pectoralis major myocutaneous flap—A versatile flap for reconstruction in the head and neck. Plast Reconstr Surg 63:73-81, 1979

47. McGraw JB, Dibbell DG, Carraway JH: Clinical definition of independent myocutaneous vascular territories. Plast Reconstr Surg 60:341-352, 1977

48. Owens NA: A compound neck pedicle designed for the repair of massive facial defects: Formation, development and application. Plast Reconstr Surg 15:369-389, 1955

49. Quillen CG: Latissimus dorsi myocutaneous flaps in head and neck reconstruction. Plast Reconstr Surg 63:644-670, May 1979

50. Fara M, Smahel J: Postoperative followup of restitution procedures in the orbicularis oris muscle after operation for complete bilateral cleft of the lip. Plast Reconstr Surg 40:13-21, 1967

51. Pennisi VR, Shadish WR, Klabunde EH: Orbicularis oris muscle in the cleft lip repair. Cleft Palate J 6:141-153, 1969

52. Kriens O: Anatomy of the velopharyngeal area in cleft palate. Clin Plast Surg 2:261-283, 1975

53. Stool S, Randall P: Unexpected ear disease in cleft palate patients. Cleft Palate J 4:99-103, 1967

54. Johanssen B: Lessons learned from experience in bone grafting clefts. Presented at the annual meeting of the American Society of Plastic and Reconstructive Surgeons, New Orleans, 1980

55. Blackfield HM, Torrey FA, Morris WJ, et al: Management of visible hemangiomas. Am J Surg 94:313-320, 1957

56. Apfelberg DB, Maser MR, Lash H: Argon laser treatment of cutaneous vascular abnormalities: Progress report. Ann Plast Surg 1:14-18, 1978

57. Owsley JQ Jr: Platysma-fascial rhytidectomy: A preliminary report. Plast Reconstr Surg 60:843-850, Dec 1977

58. Rees TD: Current concepts in rhinoplasty. Clin Plast Surg 4:131-144, 1977

Specialty Conference

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LT NORMAN WAECKER, MC, USNR
WILLIAM L. NYHAN, MD, PhD

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Refer to: Koenig HM, Stein MT, Waecker N, et al: Neutropenia of childhood—University of California Medical Center, San Diego, and Naval Regional Medical Center, San Diego (Specialty Conference). West J Med 136:29-34, Jan 1982

Neutropenia of Childhood

MARTIN STEIN, MD:* A complete blood count may give unsuspected findings in a child with an acute illness. Anemia or thrombocytopenia may be an incidental discovery. Less often, significant abnormalities in the white cell series may uncover an important disease process.

In a child with an infectious process, a complete blood count is indicated in order to evaluate the effects the infection has on the bone marrow and the circulating blood elements. The case report presented at this conference illustrates the potential value of a complete blood count in a child with an uncommon, though not rare, infection and gives a clinical approach to the appropriate diagnosis.

LT NORMAN WAECKER, MC, USNR:† A 24-month-old white boy presented with a five-day history of an upper respiratory tract infection and temperature rising to 39.1°C (102.4°F). He had bilateral otitis media and was treated with penicillin and sulfasoxizole. The fever continued over the next three days, with the temperature increasing to 40.5°C (105°F). The infant was seen again in the outpatient clinic and was noted to have left periorbital cellulitis. A blood count showed neutropenia and the child was admitted to hospital. There were no known exposures to chemical or toxic materials. Medications were limited to penicillin, sulfasoxizole and acetaminophen. He had had numerous previous upper respiratory tract infections and five episodes of acute otitis media.

Are there any questions?

PHYSICIAN IN THE AUDIENCE: *Had he had previous white counts?*

DR. WAECKER: None were recorded on the chart.

PHYSICIAN IN THE AUDIENCE: *What were the previous episodes of acute otitis media treated with?*

DR. WAECKER: Penicillin and gantrisin.

PHYSICIAN IN THE AUDIENCE: *Was anyone else at home ill?*

DR. WAECKER: No.

PHYSICIAN IN THE AUDIENCE: *Were there normal findings on an ear examination when he was checked after the last infection?*

DR. WAECKER: Yes, examination showed the tympanic membranes to have normal appearance and mobility.

PHYSICIAN IN THE AUDIENCE: *Was there any family history of recurrent or unusual infections?*

DR. WAECKER: No.

On physical examination the child was alert. The left periorbital tissues were noted to be swollen and discolored. The temperature was 38.4°C (101.1°F), pulse 128 per minute and respiratory rate 26 per minute. The blood pressure was 122/68 mm of mercury. Movement of the extraocular muscles was intact. The pupils were equally round and reactive to light. The conjunc-

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tivae and sclerae were normal, and there was no evidence of proptosis. The tympanic membranes were dull, and they had indistinct landmarks and reduced mobility bilaterally. There was a clear watery, mucoid nasal discharge. There was no palpable lymphadenopathy. There were no meningeal signs. The remainder of the physical examination showed no abnormalities.

PHYSICIAN IN THE AUDIENCE: *Could you describe the discoloration about the eye?*

DR. WAECKER: The tissues were generally hyperemic; they were reddish with a suggestion of a bluish discoloration along the medial canthus.

PHYSICIAN IN THE AUDIENCE: *When you say no lymphadenopathy, do you mean there were no palpable nodes?*

DR. WAECKER: There were some small anterior cervical nodes that appeared not to be acutely inflamed.

WILLIAM L. NYHAN, MD, PHD:* There seem to be no further questions about the history and physical examination. Let us proceed to develop a differential diagnosis.

DR. STEIN: Early in the discussion of a differential diagnosis (Table 1), the participants recognized two distinct, though possibly related, diseases: periorbital cellulitis and neutropenia. This toddler's infection was more consistent with periorbital cellulitis than orbital cellulitis. The former infection is limited to the preseptal (or anterior) region of the globe while the orbital inflammation involves the postseptal (or posterior) region of the globe. Clinically, this distinction can be made by an appreciation that proptosis, chemosis and limitation of extraocular muscle movement reflects postseptal inflammation characteristic of orbital cellulitis. The absence of these signs in the patient suggested periorbital cellulitis. Recently, the two processes have been distinguished by means of orbital computed tomographic scanning.[1] The audience also recognized the organisms likely to be causative of this clinical entity are *Staphylococcus aureus* or *Hemophilus influenzae,* although other pyogenic organisms occasionally cause this infection.[2] The slight blue discoloration described over the inner canthus suggested an infection with *H influenzae.*

As the participants in the conference turned to the differential diagnosis of neutropenia, several specific categories of disease were considered. Processes in which there is replacement or disease of the bone marrow such as leukemia and aplastic anemia were mentioned initially, presumably because of the serious nature of these diseases and their common occurrence in hospital populations. Infections themselves may cause either an increase or decrease of white cell elements, and the physicians at the conference considered bacteremia, associated with periorbital cellulitis, as a potential cause of neutropenia. Genetic forms of neutropenia were considered under two categories—familial and chronic benign neutropenia. The patient had been receiving antibiotics which suggested the possibility of a drug-induced neutropenia. The Schwachman-Diamond syndrome consists of exocrine pancreatic insufficiency in association with bone marrow dysfunction. Patients with this disorder usually have retardation of growth, malabsorption and an increased susceptibility to infection due to a fluctuating neutropenia. Other less common childhood diseases that may suppress the leukocyte count include neuroblastoma, Gaucher's disease and the organic forms of acidemia, which include isovaleric acidemia, propionic acidemia, methylmalonic acidemia, multiple carboxylase deficiency and glutaric aciduria type II.

TABLE 1.—*Differential Diagnosis**

Problem No. 1:	
Periorbital Cellulitis	
Due to:	*Staphylococcus aureus*
	Hemophilus influenzae
	Streptococcus
Problem No. 2:	
Neutropenia	
Due to:	Aplastic anemia
	Leukemia
	Viral infection
	Bacteremia
	Familial neutropenia
	Drug-induced neutropenia
	Schwachman-Diamond syndrome
	Organic acidemia
	Neuroblastoma
	Gaucher's disease
	Chronic benign neutropenia

*Compiled by physicians in the audience. See text.

PHYSICIAN IN THE AUDIENCE: *What were findings on the complete blood counts done on admission and during the hospital course?*

DR. WAECKER: Serial leukocyte counts were done in the hospital. On the day of admission the total count was 7,900 leukocytes per cu mm and the

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absolute granulocyte count 247 per cu mm. He was treated with ampicillin and oxacillin and there was rapid defervescence. After eight days there was no evidence of otitis media or periorbital cellulitis. Cultures of the blood and cerebrospinal fluid for bacteria were negative.

PHYSICIAN IN THE AUDIENCE: *The next step in this child's evaluation would be to carry out a bone marrow aspiration.*

DR. WAECKER: The bone marrow was normal. We called on Dr. Harold Koenig to help us understand and manage this case. Let me ask him to explain his analysis of the problem.

CAPT HAROLD M. KOENIG, MC, USN:* Neutropenia in childhood represents a mixed group of disorders, many of them poorly understood. The differential diagnosis developed is very complete (Table 1).

As a background for a more precise diagnosis, it is important to review the kinetics of the granulocytes and some information about normal granulocyte counts. In a newborn infant born after more than 32 weeks of gestation, the average granulocyte count is about 8,000 per cu mm. From about 1 to 2 months of age up to 1 year, a granulocyte count below 2,500 would be considered abnormal.[3] From that point on, anything under 1,500 would be considered an abnormally low absolute granulocyte count. A common exception to this rule is that about 30 percent of black people have absolute granulocyte counts as low as 300 per cu mm. The reasons for this are not completely understood, but it has been postulated that in these persons there are decreased marrow granulocyte storage pools.[4]

This patient was a white child. His absolute granulocyte counts on seven occasions over a period of a month were all quite low. This has direct consequences for the occurrence of infectious disease. If the absolute granulocyte count drops below 1,000 cells per cu mm, the chances of something like stomatitis, cellulitis or periorbital cellulitis developing (as in this patient) increase. When the absolute granulocyte count dips below 500 cells per cu mm, especially without a concomitant brisk monocytosis, the chances of a severe, deep seated bacterial infection or bacterial sepsis developing become quite real.

From the point of view of granulocyte kinetics, granulocytes are derived from pleuripotent stem cells. Granulocytes undergo some three to five nuclear divisions as they progress from the myeloblast to the myelocyte stage. The process of maturation takes seven to eight days. From the myelocyte stage of development to the mature polymorphonuclear cell no further nuclear divisions occur. This process takes another three to five days. Once the cell becomes mature, it spends one or two days in the bone marrow and then six to eight hours in the peripheral circulation. The polymorphonuclear cell then moves into the tissues where it remains up to four days, prepared to combat infection. The maximum total life span of a granulocyte is about 18 days.[5] Unfortunately, effective methods for assessing granulocyte kinetics in many laboratories are not available. The tools generally available are the peripheral blood count and the bone marrow aspiration. A study of this boy's bone marrow found it to be very cellular. There were normal numbers of erythroid elements. Myeloid precursors were also abundant in the bone marrow. The myeloid:erythroid ratio was greater than normal. This indicated that his marrow was making plenty of granulocytes.

There are a variety of approaches to neutropenia in children. Primary care clinicians may approach the problem by considering various diagnostic categories; the differential diagnosis developed in Table 1 is a fine example of this method. An alternative approach is to develop a classification based on the physiology of granulocyte kinetics. Such an approach was proposed by Stuart Finch[6] in William's textbook *Hematology,* an excellent reference on this subject. Neutropenia in childhood has been recently reviewed by Wheetman and Boyer.[7] Following Finch's classification, type I neutropenia is that in which there is decreased production of granulocytes (Table 2). Type II neutropenia is that in which production is ineffective; that is, granulocytes are being made, but they are not getting out of the bone marrow and getting into circulation. In this kind of situation, when the bone marrow is examined, an arrest of maturation is often found. The third type of neutropenia is a consequence of decreased survival. In this situation, there are increased numbers of granulocytes in the bone marrow, decreased numbers in the peripheral blood and decreased survival. It is possible to label granulocytes, inject them into a patient and determine how long they survive, but obtaining

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TABLE 2.—*Functional Classification of Granulocytopenia*

I	Reduced granulocytopoiesis Decreased marrow myeloid precursors
II	Ineffective granulocytopoiesis Increased marrow myeloid precursors with intermedullary destruction
III	Decreased granulocyte survival Increased marrow myeloid precursors with increased peripheral destruction or utilization
IV	Combination (type I or II, plus III)
V	Pseudoneutropenia Normal granulocytic pool with shift from circulating to marginating pool

reproducible data is difficult. Type IV neutropenia may be considered a combination usually of types I and III. Decreased production along with decreased survival is commonly seen in drug-induced neutropenia. Type V comprises forms of pseudoneutropenia, in which the person is not really neutropenic.

Examples of type I include the Schwachman-Diamond syndrome and the Costman syndrome, which is congenital agranulocytosis. There are other disorders that have been defined as defects causing decreased production. Separating one from the other depends on the type of associated anomalies found in the patient. There are chronic severe forms of neutropenia that result from decreased production, and there are chronic benign forms. Both benign and severe forms have been documented to be familial. Ineffective production may be seen in patients who have received chemotherapy, especially folic acid antagonists such as methotrexate, or in people with severe deficiency of vitamin B_{12} or folate. Decreased survival is seen in isoimmune neutropenia of infancy, or in autoimmune neutropenia, or in drug induced disease. Many different types of neutropenia are drug related. Viral, bacterial and protozoal infections can produce type I defects.

Pseudoneutropenia includes disorders in which the person has an inability to mobilize granulocytes at a normal rate from the bone marrow, has an increased storage pool or has an increased marginating pool. About half of a normal person's granulocytes marginate on the vascular lining. An injection of epinephrine in a normal person usually will double the granulocyte count in 10 to 15 minutes. There are people who supermarginate. They keep a large portion of cells in the marginating pool.

Hypersplenism was excluded as a diagnostic possibility by the physical examination of this child. Hypersplenism is not very common in childhood. It is more common in adults, but it does occur in children. In this situation there are trapped granulocytes and other elements of the blood in the spleen.

To return to this patient, in follow-up observation he did well. His marrow remained normal. Clearly this permitted us to exclude a type I neutropenia. When we did an epinephrine stimulation test, the total leukocyte count rose to 13,700 per cu mm and the percentage of polymorphonuclear forms increased from 2 percent to 14 percent and the band forms from 1 percent to 6 percent. The absolute granulocyte count rose from 250 to 2,740 per cu mm, a tenfold increase. Our conclusion was that the patient was supermarginator who simple had more cells lining his vascular endothelium than the usual person. There is some likelihood that he will outgrow this as he gets older.

PHYSICIAN IN THE AUDIENCE: *Do you believe that the frequent episodes of otitis media were related to the neutropenia?*

DR. KOENIG: I do not think so. We see many children who have normal granulocyte counts who have as much otitis as this patient.

QUESTION FROM THE AUDIENCE: *Do you think that in this patient meningitis or something else serious is likely to develop?*

DR. KOENIG: I do not think so. I believe he will do well. He had a really low absolute granulocyte count. The highest he achieved by himself was 800 cells per cu mm, but he did respond when tested appropriately.

PHYSICIAN IN THE AUDIENCE: *If a bacterial infection or sepsis develops in a normal person, the granulocyte count increases. Is part of the cause of the increased granulocyte count the patient's own outpouring of epinephrine?*

DR. KOENIG: No, I think that most of that is due to cells entering the circulation from the storage pool. There are really many reasons that granulocytes leave the storage pools and enter the circulation. We can make it happen with pharmacologic agents. It has been proposed that a substance known as colony stimulating factor may play a role in this release.

PHYSICIAN IN THE AUDIENCE: *Is the patient's problem familial?*

DR. KOENIG: We do not really know. In this

TABLE 3.—*Guidelines for the Utilization of the Total and Differential Leukocyte Count in General Pediatric Practice*

Infections—to assist in diagnosis
Neonatal sepsis
Bacteremia versus viremia
Viral versus bacterial focal process
Osteomyelitis versus trauma
Pyogenic arthritis versus noninfectious joint disease
Borderline acute surgical abdomen
Appendicitis versus mesenteric adenitis
Clinical suspicion of
Chronic inflammatory bowel disease
Collagen vascular disease
Hematologic malignancy
Monitoring
Chronic drug therapy
Sulfanamides
Trimethoprim-sulfamethoxasole
Chloramphenicol (acute or chronic therapy)
Carbenicillin
Cephalosporins
Penicillins
Antithyroid agents
Diuretics
Anticonvulsants
Phenothiazines
Radiation therapy
Chemotherapy

instance we did not have a family to study. The child was cared for by persons other than his parents.

DR. STEIN: There are two well-defined genetic patterns of neutropenia—an autosomal recessive form and an autosomal dominant form. The recessive form usually is more severe; it is manifested by recurrent baterial infections, usually of the skin and respiratory tract.

PHYSICIAN IN THE AUDIENCE: *Because this child had a potentially serious bacterial infection, complete blood count was done and the neutropenia discovered. In the office practice of pediatrics, working with children not in a hospital, I order this test only occasionally. Are there guidelines in this area?*

DR. STEIN: When a clinician suspects anemia or thrombocytopenia, the indications for the investigation of the hemoglobin or platelet count are clear. Indications for a leukocyte and differential count are not as well defined. Clinical investigators have attempted to show the utility of either leukocytosis or an absolute neutrophilia as a predictor of bacterial disease. Most of the recent pediatric studies have been of patients with neonatal sepsis[8] and children younger than two years old with fever and occult bacteremia.[9] Although an elevated leukocyte count and a shift to the left suggest bacterial disease, the predictive value is low. Nevertheless, some guidelines have emerged from experience in practice. Table 3 provides a compilation that I have developed of ways in which the leukocyte and differential counts may give clues to a general or specific diagnosis or may be used to monitor special patients.

DR. NYHAN: This specialty conference illustrates the format of the weekly Saturday Pediatric Conference at the University of California, San Diego. The current form represents a joint development by its many participants over the past 12 years. Our design is to teach problem solving rather than content. Of course a considerable amount of content is the inevitable result and this is a secondary benefit, but the emphasis is on process. We seek to reproduce the situation the clinician faces in an office and in hospital by presenting all of the cases as unknowns. The patient material is drawn from each of the institutions in San Diego concerned with our cooperative effort in the teaching of pediatrics to medical students or residents. The patient discussed in this conference was admitted to the US Naval Regional Medical Center, San Diego. A few pediatricians practicing in San Diego present patients seen in their practices. An occasional, forewarned visitor may bring a problem of a patient studied elsewhere. This breadth of sources ensures that the patient has been seen previously by very few members of the audience. The audience is a mixed group that includes medical students, house officers, fellows, full-time staff of community hospitals and pediatricians in private practice. In each group there are a number of regulars who would not miss a conference except for a serious commitment elsewhere, as well as more intermittent attendees.

The audience is encouraged to think through the problem as it develops. Key details of the history and physical examination are written on the blackboard for reference; and questions are encouraged at each step. Once the details of the history and physical examination are thoroughly explored, the audience is required to think through and develop aloud a differential diagnosis that is written on the blackboard. This is always the work of a large segment of the audience. Anyone may challenge a person suggesting a diagnosis to explain the logic of the suggestion. Occasionally, the proposer will provide this information

spontaneously, if the logic does not appear self-evident. Once the audience has committed itself on the diagnosis, the problem is worked through, again jointly, with each laboratory test or component of the workup being asked for expressly by someone in the audience. A person asking for an x-ray study may end up having to read it himself, or there may be an expert present. In this conference the neutropenia was a major argument for the admission. Therefore, the workup available to nonexperts was limited. Once it was apparent that the marrow was normal, consultation was required. This process has been detailed in a comprehensive fashion by Dr. Koenig.

REFERENCES

1. Goldberg F, Berne AS, Oski FA: Differentiation of orbital cellulitis from preseptal cellulitis by computed tomography. Pediatrics 62:1000-1005, 1978

2. Smith TF, O'Day D, Wright PF: Clinical implications of preseptal (periorbital) cellulitis in childhood. Pediatrics 62:1006-1009, 1978

3. Coulombel L, Dehan M, Tchernia G, et al: The number of polymorphonuclear leukocytes in relation to gestational age in the newborn. Acta Pediatr Scand 68:709-711, Sep 1979

4. Broun GO Jr, Herbig EK, Hamilton JR: Leukopenia in Negroes. N Engl J Med 275:1410-1413, 1966

5. Athens JW: Neutrophilic granulocyte kinetics and granulocytopoiesis, *In* Gordon AS (Ed): Regulation of Hematopoiesis, Vol II. New York, Appleton-Century Crofts, 1970, p 1143

6. Finch SC: Granulocytopenia, *In* Williams WJ, Beatler E, Ersley AJ, et al (Eds): Hematology, 2nd Ed. New York, McGraw-Hill Book Co, 1977, pp 717-746

7. Wheetman RM, Boyer LA: Childhood neutropenia. Ped Clin N Am 27:361-375, 1980

8. Christensen RD, Bradley PP, Rothstein G: The leukocyte left shift in clinical and experimental neonatal sepsis. J Pediatr 98: 101-105, 1981

9. McCarthy PL, Jekel JF, Dolan TF: Temperature greater than or equal to 40°C in children less than 24 months of age: A prospective study. Pediatrics 59:663-668, 1977

Refer to: Ross TF: Health care problems of Southeast Asian refugees—Medical Staff Conferences, University of California, San Francisco. West J Med 136:35-43, Jan 1982

Health Care Problems of Southeast Asian Refugees

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *At this time of year, it is customary to invite our chief residents to present Medical Grand Rounds. This enables us to express publicly our appreciation for the superb leadership they have provided our teaching and patient care program. Dr. Tom Ross will speak on health care problems of Southeast Asian refugees. During his senior residency year, Dr. Ross spent six weeks as a volunteer physician in a refugee camp in Thailand. He will begin his discussion by presenting a case.*

DR. ROSS:† The patient is a 63-year-old man from Kampuchea (formerly Cambodia) who was admitted to the Khao I Dang Refugee Camp hospital located on the Thailand-Kampuchea border. He was in his usual state of health until shortly after he arrived at the camp three months previously. A progressive cough productive of blood-tinged sputum developed, and he experienced weight loss, malaise and episodic fever with night sweats. He was taking no medications and had no past history of pulmonary disease.

Physical examination showed a cachectic-appearing elderly man in moderate respiratory distress. Temperature was 38.4°C (101°F), blood pressure 90/50 mm of mercury, pulse 115 beats per minute and respirations 28 per minute. His weight was 40 kg (88 lb) and height 168 cm (5 ft 6 in). Subcutaneous fat appeared absent and there was pronounced diffuse muscle wasting. The conjunctivae were pale and the neck was supple. Pulmonary findings included bilateral dullness to percussion, bronchial breath sounds and rales. All findings were more prominent on the left. A grade II/VI systolic ejection murmur was heard at the lower left sternal border. The liver was nontender and 11 cm in span. The spleen was not palpable. There was no peripheral edema, cyanosis or clubbing seen. No abnormal neurologic findings were detected.

Results of laboratory tests were as follows: hematocrit 12 percent and leukocyte count 11,400 per cu mm, with 55 percent granulocytes, 12 percent eosinophils, and 25 percent lymphocytes. The peripheral blood smear showed prominent microcytosis and hypochromasia. No malarial parasites were seen. Roentgenogram of the chest (Figure 1) showed bilateral parenchymal infiltrates in all lung fields. Kinyoun stain of sputum specimen showed numerous acid-fast bacilli (AFB). Examination of stool revealed numerous hookworm ova, a moderate number of *Ascaris* ova and rare *Strongyloides* larvae.

The primary diagnosis on admission was pulmonary tuberculosis and treatment was started

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†Thomas F. Ross, MD, Chief Resident in Medicine.

ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
BCG = bacille Calmette-Guérin
CDC = Centers for Disease Control
HBsAg = hepatitis B surface antigen
PPD = purified protein derivative
PVA = polyvinyl alcohol

with isoniazid (INH), ethambutol and streptomycin. The protein-calorie malnutrition and anemia were treated with supplemental feedings, vitamin replacement and parenteral iron. Mebendazole was given for hookworm and *Ascaris* but the *Strongyloides* infection was not treated. On this regimen there was gradual clinical improvement with a decrease in pulmonary symptoms and by the seventh hospital day the patient was afebrile. There was a steady increase in weight and hematocrit.

On the 18th hospital day his temperature rose to 41°C (105.8°F), and he had headache and low back pain. Results of a lumbar puncture were negative. A peripheral blood smear showed 10 percent parasitemia with *Plasmodium falciparum*. Treatment was begun with pyrimethamine and sulfadoxine with good clinical response and a peripheral blood smear several days later was free of parasites.

On the 24th hospital day his temperature again rose to 40°C (104°F) and peripheral blood smear showed 2 percent parasitemia, this time with *Plasmodium vivax*. Therapy was instituted with chloroquine hydrochloride, again with a good response. The remainder of the patient's hospital course was uncomplicated and he was discharged after 1½ months.

Discussion

This discussion will review the major medical problems that have been reported of Indochinese refugees settling in the United States.[1-5] If the case just described is typical, we might expect to see a variety of infectious diseases including tuberculosis, intestinal parasites and malaria. Additional expected disorders (Table 1) include anemia, malnutrition, inadequate immunizations and a variety of psychiatric and cultural problems.

Between 1975 and March 1981, 475,000 refugees entered this country from Southeast Asia. It is estimated that 35 percent of these persons have settled in California. Potential medical problems in this group are thus of considerable interest to health care providers in this state. This exodus of refugees has been the result of an unstable political situation involving several countries in Southeast Asia. A demographic analysis of 155,000 refugees who arrived in 1980 reveals a predominantly young population with a median age of 20 years;[6] 37 percent of the population was under the age of 15 and only 9 percent was over 45. About 53 percent of the refugees who arrived during that period were born in Vietnam, 34 percent in Laos and 6 percent in Kampuchea.

Before analyzing the health care problems of refugees after arrival in this country, it is instructive to review their experiences before immigration. After fleeing their countries of origin by boat or land, they enter refugee camps in Thailand, Indonesia and Malaysia. There they remain for six months to five years before resettling in

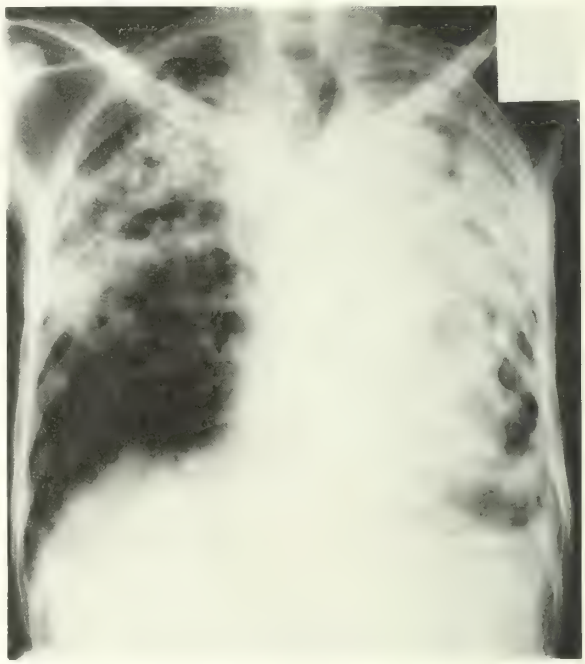

Figure 1.—Roentgenogram of chest showing bilateral parenchymal infiltrates.

TABLE 1.—*Major Medical Problems Among Indochinese Refugees*

Infections
Tuberculosis
Intestinal parasites
Malaria
Hepatitis carriers
Other—skin, respiratory
Anemia
Malnutrition
Poor immunization status
Psychiatric and cultural problems

another country. The crowded conditions and poor medical facilities of these camps have been widely publicized in recent years.[7,8] A typical refugee camp is that of Sa Kaeo located in Thailand near the Kampuchea border.[9,10] Opened in late 1979 it quickly swelled to a population of 32,000. During a three-week period in November 1979 the field hospital recorded 2,342 admissions and 144 deaths. Fever and malaria, pneumonia, anemia, malnutrition and diarrhea were responsible for 69 percent of these admissions and deaths. Surveys of the camp revealed evidence of considerable malnutrition in 14 percent of children. Screening for malaria showed a prevalence of 38 percent. Reports from other camps showed variation in the incidence of malaria and other diseases, but in general corroborated the findings of a multitude of major medical problems with high mortality.[11]

The influx of outside assistance with improved nutrition and medical care had a noteworthy impact on these problems, evidenced by a fall in crude death rates.[12] In early November 1979 the death rate in several camps in Thailand was as high as 1.05 per 1,000 persons per day. By mid-December of that year mortality had dropped to 0.025 per 1,000 persons per day, a level considered no greater than that in Kampuchea and Laos before the present conflict. Current reports from refugee camps continue to document the stability of the death rate and control of major medical problems.

After a variable period refugees apply for resettlement in a third country. Entry requirements to the United States include a medical examination for tuberculosis, leprosy, venereal disease and mental disorders. Persons with these conditions in an active or infectious stage are excluded from entry.[1] The effectiveness of screening for acute medical problems is shown by the results of a study conducted by the Centers for Disease Control (CDC).[13] At their points of entry into the US 4,324 refugees were evaluated for acute medical problems. Fever was found in only 1.7 percent and clinical evidence of pneumonia in less than 0.1 percent. Immediate admission to hospital was necessary in 0.1 percent and prompt outpatient medical attention was required at their eventual destination in only 2.2 percent of these refugees.

Tuberculosis

In 1979, 920 cases of tuberculosis were reported in refugees, with a prevalence of 0.9 percent. In the first six months of 1980 an additional 1,272 cases were reported, with a prevalence of 1.1 percent.[14] Although the 920 cases in 1979 represented only 3.4 percent of the tuberculosis reported in the US, in some states the refugees accounted for a relatively large proportion of the cases. Tuberculosis in refugees accounted for 18 percent to 27 percent of all cases in Washington, Colorado, Nevada and Minnesota, and for 10 percent of cases in California. Prevalence rates by country of origin range from 0.4 percent in Laotians to 1.5 percent in Kampucheans. The prevalence in refugees also varies with age and sex. In individuals under the age of 15 the rate is 0.4 percent, but in persons over the age of 45 this rate is greater than 2.7 percent. Tuberculosis occurs 1½ times more frequently in males than in females. Overall, the relative risk of tuberculosis among Indochinese refugees is 38 times that for a US citizen.

TABLE 2.—*Organ System Involvement in Tuberculosis*

Organ System	*Refugees, 1979*[11] *(percent)*	*United States, 1976*[15] *(percent)*
Pulmonary	90	86
Extrapulmonary	10	14
Lymphatic	52	25
Pleural	18	22
Bone/joint	9	9
Genitourinary	7	18
Miliary	2	8
Meningeal	2	4
Peritoneal	2	3
Other	8	11

As shown in Table 2 organ-system involvement in tuberculosis is similar in refugees and in the general US population, with 85 percent to 90 percent of cases involving the lungs.[15] One exception to this is a twofold increase in lymphatic involvement. This is best explained by the young age of refugees and a recognized increase in lymphatic involvement in younger persons with tuberculosis.[16] The consumption of unpasteurized milk may also play a role.

Screening of refugees for tuberculosis before entering this country consists of a roentgenogram of the chest and a sputum smear for acid-fast bacteria. Chest x-ray films are obtained in all persons over 2 years of age except in Singapore and Indonesia where they are obtained in persons 15 years or older. Sputum smears are obtained in persons with roentgenograms of the chest reported as abnormal. Based on results of these tests refugees are certified in one of three categories:

(1) active or suspected disease—class A; (2) nonactive disease—class B, and (3) no evidence of disease—not classified.

Class A, active or suspected-active disease, is determined by a chest roentgenogram reported as abnormal, associated with a sputum smear showing the disease or a compatible clinical condition (or both). Persons so certified are excluded from entering the US until the disease is considered inactive or noncontagious, documented by two negative smears for AFB taken at least a day apart. Recommended treatment before entry consists of isoniazid (INH), rifampin and ethambutol in persons with a smear read as positive or a cavitary lesion seen on roentgenogram of the chest (or both). Other persons classified in this category (that is, those with smears reported as negative but with a clinical condition compatible with tuberculosis) can be started on treatment with the three drugs or treatment can be deferred until after arrival in the US.

The use of three antituberculosis drugs is recommended on the basis of resistance patterns of Indochinese refugees. An ongoing study of primary resistance of antituberculosis drugs is being conducted by the CDC.[17] As of July 1980 7.1 percent of all *Mycobacterium tuberculosis* organisms isolated from persons in the US were resistant to at least one drug. In Asian persons the resistance rate was 12.7 percent, chiefly to isoniazid and streptomycin. Preliminary reports in Indochinese refugees reveal resistance rates between 15 percent and 40 percent for these two drugs. Because of this high rate of primary resistance the use of three-drug therapy is warranted in all Indochinese refugees pending results of sensitivity studies.

After arrival in the US, specimens for culture and sensitivity should be obtained from all persons categorized as class A. Treatment with isoniazid, rifampin and ethambutol should be continued, or started in those persons not already on therapy, pending results of sensitivity tests. Persons with a culture positive for tuberculosis should continue to take two drugs for at least 12 months after smears have been reported negative. Those with cultures reported as negative should continue on three drugs for a minimum of 12 months.

Class B includes those persons considered to have nonactive tuberculosis. This is defined by abnormal findings on roengenogram of the chest associated with two sputum cultures negative for AFB. These persons are considered noncontagious for travel purposes and treatment is not necessary before entry. After arrival in this country, their status should be reevaluated. Roentgenograms of the chest should be reviewed and sputum specimens obtained for smear and culture. If found to have active disease, treatment with three drugs should be started as in class A. Persons with nonactive disease should be considered for preventive therapy with isoniazid.

Those persons with a normal roentgenogram of the chest and no clinical evidence of tuberculosis are not classified. There is no effect on immigration and consequently no treatment is recommended. Follow-up care after arrival should include a review of the roentgenogram of the chest and purified protein derivative (PPD) placement if the person is under age 35.

Given the above classification we can examine the effectiveness of overseas screening for active tuberculosis by reviewing the 920 cases reported in 1979. Of these, 27 percent were persons certified as class A, 20 percent class B, and 18 percent neither. In the remaining 35 percent, overseas classification was unknown. When the total number of persons in each of these categories is compared, the prevalence of current tuberculosis in refugees certified as class A becomes 61 percent and class B 14 percent. Only 0.3 percent of those persons considered to have no evidence of tuberculosis were later found to have evidence of active disease in this country. Thus current screening procedures appear reliable in identifying high-risk groups.

Preventive therapy is recommended for persons in contact with patients with active disease. Studies of the PPD status of refugees are 30 percent positive in persons under age 18 and 55 percent in persons over 18. For all age groups, 43 percent have positive PPD tests.[2,5] The PPD test should be interpreted without regard to bacille Calmette-Guérin (BCG) status. Given the lack of preventive health care in those areas of Southeast Asia during recent years and the young age of refugees, the incidence of prior BCG immunization would be expected to be low. Isoniazid should be used for prophylaxis unless there is known exposure to an isoniazid-resistant strain. In this situation options include treatment with isoniazid, treatment with rifampin with or without isoniazid or no treatment but with close follow-up. There are insufficient data to support the superiority of any of these options.

TABLE 3.—*Malaria in California*

	1979		1980		1981 (1st quarter)		All U.S.	
	No.	Percent	No.	Percent	No.	Percent	1979	1980
Total cases	318		743		152		..	
Refugee cases	41	13	437	59	101	66	..	
Plasmodium vivax		(71)		(90)		(95)		75
Plasmodium falciparum		(20)		(5)		(0)		15
Plasmodium malariae		(5)		(3)		..		..

Adapted from *California Morbidity #10*.[21]

Before leaving this topic, it is important to mention two clinical illnesses reported in refugees that may mimic tuberculosis, melioidosis[18] and paragonimiasis.[19] These disorders should be suspected in persons with findings on roentgenogram of the chest and clinical features consistent with tuberculosis, but with a negative PPD response, a positive PPD response but negative culture and smear for AFB, or a poor response to adequate antituberculosis therapy. Melioidosis is an infection caused by a Gram-negative bacillus, *Pseudomonas pseudomallei*. Diagnosis is made on the basis of Gram stain and culture. Serologic tests provide supportive evidence. Successful treatment has been reported with a variety of antibiotics including tetracycline, chloramphenicol, sulfisoxazole and trimethoprim-sulfonamide for a minimum of 30 to 60 days. Paragonimiasis is caused by the lung fluke *Paragonimus westermani*. Diagnosis is suggested by eosinophilia and confirmed by the identification of characteristic eggs in the sputum and feces and on serologic tests. Treatment consists of biothionol, 30 mg per kg of body weight, taken orally on alternate days for a total of ten doses.

Malaria

During the past several years there has been a sharp increase in the number of reported cases of malaria in refugee groups. During the first six months of 1979, 163 cases of malaria were reported in the US, 20 percent of these in Southeast Asian refugees. During the same period of 1980, 553 cases were reported, 64 percent in Indochinese refugees.[20] Similar findings have been described in California,[21] as shown in Table 3. Between 70 percent and 95 percent of reported cases have been *Plasmodium vivax* and most of the rest are *Plasmodium falciparum*. Cases of *Plasmodium malariae* have occurred sporadically.

The prevalence of malaria in Southeast Asian refugees can be estimated from the results of several screening studies.[20] Using an indirect fluorescent antibody technique as an indicator of past or present infection, it was determined that 11.4 percent of refugees had been infected with *P falciparum* and 4.8 percent with *P vivax*. When blood smears were examined for parasitemia it was found that 1.2 percent of refugees had *P vivax* and 0.4 percent had *P falciparum*. Thus by fluorescent antibody techniques, infection with *P falciparum* had a prevalence of almost 2½ times that of *P vivax;* yet, with respect to parasitemia, *P vivax* was more prevalent by 3 to 1. This probably reflects previous adequate schizonticidal therapy that eliminated most *P falciparum* infections but did not eliminate the exoerythrocytic phase of *P vivax*. Thus a substantial number of clinical *P vivax* relapses may appear in the future.

The clinical diagnosis of malaria should be considered in any refugee with fever. It is important to differentiate the organism because of therapeutic implications. *P falciparum* infections must be identified because extremely high degrees of parasitemia can be reached, causing death through the complications of severe anemia, renal failure, cerebral dysfunction and pulmonary edema. Few clinical findings permit this differentiation, though most cases of *P falciparum* have been reported within seven weeks after arrival in the US. Several morphologic criteria allow the nonparasitologist to differentiate species by examination of the peripheral blood smear. Infections with *P falciparum* show multiple infected erythrocytes of normal size with schizonts rarely seen. The banana-shaped gametocyte is diagnostic. *P vivax* is distinguished by the fewer number of infected erythrocytes that are enlarged in size and the presence of Schüffner's dots.[22]

Initial therapy pending laboratory confirmation of species should be based on clinical assessment. A seriously ill patient should be started on quinine sulfate taken orally for *P falciparum*.

TABLE 4.—*Prevalence of Intestinal Parasites in Southeast Asian Refugees*

	Study Prevalence by Percent						
	Erickson and Hoang[2]	*Morbidity Mortality Weekly Report*[5]	*Jones, Thompson and Brewer*[26]	*Temcharoen Viboolyavantana and Wanaratana*[27]	*Wiesen-et al.*[28]	*Calif. Morbidity #13*[29]	*Mahmoud*[33] *All U.S.*
Hookworm	21	7	16	18	64	6	0.3
Ascaris	21	12	41	13	9	17	2
Strongyloides	3	1	1	4	..	3	0.2
Trichuris	10	9	30	14	12	5	1
Enterobius	..	..	2	> 1	..	> 1	21
Clonorchis	9	2	2	..	..	1	..
Hymenolepsis	..	..	..	> 1	..	> 1	0.05
Entamoeba histolytica	..	1	6	2	..	> 1	3-4
Giardia lamblia	9	4	15	6	18	2	2-7
Total prevalence of one or more parasites	65	15	76	67	78	35	..

Patients who cannot take medications orally should have quinine hydrochloride administered intravenously. Clinically stable patients can be observed or started on chloroquine hydrochloride. Confirmed cases of *P vivax* are treated with chloroquine (base): 600 mg initially, then 300 mg at 6, 24 and 48 hours.[1,23] This should be followed with an aggressive regimen (to eliminate the exoerythrocytic parasites) using primaquine phosphate (base): 15 mg daily for 14 days or 45 mg weekly for eight weeks.[24] Treatment of *P malariae* is similar to *P vivax* except the aggressive regimen is not required.

There are three oral regimens for the treatment of *P falciparum*:[1,23] (1) quinine sulfate, 650 mg three times a day for three days, plus pyrimethamine, 25 mg twice a day for five days, plus sulfadiazine, 500 mg three times a day for five days—all drugs administered concurrently; (2) quinine sulfate, 650 mg three times a day for three days, plus trimethoprim, 160 mg, with sulfamethoxazole, 800 mg, 2 tablets twice a day for five days, administered concurrently; (3) quinine sulfate, 650 mg three times a day for three days, plus tetracycline, 500 mg four times a day for ten days, administered concurrently. Strains of *P falciparum* resistant to both chloroquine and pyrimethamine-sulfonamide have appeared along the Thai-Kampuchea border. Refugees from these areas should be treated with option number 3 (quinine sulfate plus tetracycline) unless contraindications exist for the use of tetracycline.[25]

In summary, because of the relatively low prevalence of malaria, routine screening is not required. In refugees with fever, suspicion is warranted and blood smears should be obtained for diagnosis and species identification. Screening for glucose-6-phosphate dehydrogenase deficiency should be obtained in all persons treated with primaquine because of an estimated 10 percent to 12 percent prevalence in Indochinese. Further, blood donation should be deferred for at least three years after entry into the US or until three years after treatment. Appropriate mosquito vectors such as *Anopheles freeborni* exist in areas of the US, so domestic transmission of malaria can occur. No such cases have been reported in relation to Southeast Asian refugees, however, which probably reflects the low prevalence and degree of parasitemia in this population.

Intestinal Parasites

A number of studies have reported the presence of multiple intestinal parasites in Southeast Asian refugees.[2,5,26-29] As shown in Table 4, there is wide variation in reported prevalence, ranging from 15 percent to 78 percent. The predominant organisms are several nematodes, *Entamoeba histolytica* and *Giardia lamblia*. Analysis of these studies reveals several factors that can account for the variations. The number of persons surveyed varied between 31 and 2,000 and included multiple ethnic groups and refugee camp locations. The number of specimens per person ranged from one to three and methods of stool preservation and examination differed. Populations studied included both asymptomatic and symptomatic groups and previous antiparasitic therapy was not determined.

The value of obtaining multiple stool specimens was demonstrated in a study performed by Lindes.[30] In this investigation the overall pre-

valence of intestinal parasites was noted to be 77 percent. The percentage of false negatives in single stool specimens when compared with results of three specimens ranges from 6 percent for hookworm to 50 percent for *E histolytica*. The importance of techniques of preservation and examination was demonstrated in a study from the Mayo Clinic.[26] In this investigation of 100 refugees, an overall prevalence of 76 percent was noted. Of the 100, 53 persons had three fresh purged stool specimens examined. The remaining 47 persons had an unknown number of stools examined after preservation in polyvinyl alcohol (PVA). There was a marked difference in the identification of intestinal parasites between these groups: a 6-percent prevalence of hookworm in the PVA stools and a 24-percent prevalence in the fresh stools. Ideally, then, a search for intestinal parasites should consist of three purged specimens examined in a fresh condition.

The rationale for treatment of intestinal parasites is based on analysis of potential public health problems and patient morbidity. Examination of Table 4 shows a substantially higher prevalence of nematode infections in refugees than in the US population as a whole and a modest increase in the prevalence of *E histolytica* and *Giardia*. Because of this, concern has been raised about the potential spread of these organisms. With few exceptions this appears unlikely because adequate sewage disposal interrupts the extended extracorporeal development stage of many nematodes, improved hygienic practices may decrease fecal-oral transmission of infective stages of parasites, and the specific intermediate hosts of several parasites are not present in this country.

Treatment of patients is based on three principles. First, morbidity is generally proportional to parasite burden.[31] Notable exceptions occur, however. Even a single *Ascaris* worm can cause significant morbidity in certain unusual situations. Second, a parasitologic cure is not necessarily the end point of therapy if the worm burden can be greatly reduced. Third, antiparasitic drugs may have unacceptable toxicity.

Treatment of many roundworm infections (hookworm, *Ascaris, Trichuris* and *Enterobius*) is with a nontoxic drug, mebendazole, at a dosage of 100 mg twice a day for three days. With this regimen, reported cures range from 75 percent to 96 percent and substantial reductions in egg count occur in greater than 95 percent of cases.[32,33] *Strongyloides* infections are treated with thiabendazole, 25 mg per kg of body weight twice a day for two days.[23] Current recommendations for *Entamoeba histolytica* include metronidazole, 750 mg three times a day for five to ten days plus diiodohydroxyquin, 650 mg three times a day for 20 days. *Giardia* can be treated with quinacrine, 100 mg three times a day for five days.[23]

Hepatitis

Concern has been voiced regarding the prevalence of hepatitis B carriers (hepatitis B surface antigen [HBsAg] positive persons) in the refugee population.[1,34] Pooling the results of four studies reveals a carrier rate of 15 percent.[2,5,26,35] In comparison the prevalence is 0.3 percent in the US as a whole and 6 percent to 7 percent in high-risk groups such as homosexual men and patients maintained on dialysis. Based on current populations, 71,000 new carriers have been added to a pool of 600,000, an increase of 12 percent. A further increase in prevalence among Indochinese appears unlikely because most refugees arrive in family groups and a high degree of immunity to hepatitis B exists in this population. High-risk groups for transmission do exist, however, and include neonates, medical and dental workers, and host families or persons in close contact with refugees. Because of this, routine screening for HBsAg is recommended.

Other Infections

Screening and treatment for syphilis before entering this country accounts for the reported low incidence, 1 percent to 5 percent of positive VDRL tests.[5,26,35] During the past several years sporadic cases and limited outbreaks of cholera, measles, diphtheria, epidemic conjunctivitis and typhoid fever have been reported in refugees.[36-39] Follow-up studies have failed to show notable secondary spread. Leprosy has been reported in only a few persons, its general prevalence unknown.[1] Skin infections (including those caused by fungus, impetigo, scabies and lice) have been reported in 7 percent to 15 percent of refugees.[2,5,35] Infections of the upper respiratory tract and otitis media have been reported in 20 percent of persons.[5,26] Also, the importation into the US of highly resistant bacteria by Southeast Asian refugees is another potential problem.[40]

Hematologic Disorders

Erickson and Hoang[2] examined 194 refugees and found eosinophilia in 47 percent, the degree

TABLE 5.—*Prevalence of Hemoglobin Disorders in Southeast Asia*

	Vietnam[42] Percent	Laos[44] Percent	Thailand[44] Percent	Kampuchea[45] Percent
Hemoglobin E	2	35	40	30
α Thalassemia	6	40	25	..
β Thalassemia	3	15	6	..
Glucose-6-phosphate dehydrogenase deficiency	3	13	15	..

TABLE 6.—*Recommendations for Vaccine Administration to Indochinese Refugees**

Age	Vaccine†
2 to 14 mo.	DTP, TOPV
15 mo. to 6 yr.	DTP, TOPV, MMR
7 to 13 yr.	Td, TOPV, MMR
14 to 19 yr.	Td, TOPV, MMR‡
20 yr.	Td

Reproduced with permission of *Morbidity Mortality Weekly Report*.[47]
DTP = diphtheria, tetanus, pertussis; Td = tetanus-diphtheria, adult type; TOPV = trivalent oral polio vaccine; MMR = measles, mumps, rubella.

*Begun in transit centers as of January 1980.
†Doses given in transit centers: 1 of MMR and first series for DTP or Td and TOPV. Additional doses in series will depend on the time spent in transit centers.
‡MMR not given to girls 14 to 19 years of age in transit centers because of unknown fertility status.

of which was greater than 10 percent in half of these persons. In light of the prevalence of parasitic infections it is not unexpected that considerable eosinophilia has been detected. Anemia has been detected in 16 percent to 40 percent of refugees with higher prevalence in young children.[5,41] The major causes include iron deficiency in 37 percent, hemoglobin disorders in 30 percent and chronic disease in 10 percent.[2] Hookworm infections are thought to be the major cause of iron deficiency. The incidence of hemoglobin disorders varies considerably between countries in Southeast Asia (Table 5). Hemoglobin E and thalassemia are the most prevalent conditions.[42-45] Hemoglobin E in the homozygous state results in a mild microcytic anemia with target cells. Based on the above, evaluation of anemia in Indochinese refugees should include examination of a peripheral blood smear, serum iron studies and possible qualitative and quantitative hemoglobin serum electrophoresis.

Malnutrition

Few studies have evaluated the nutritional status of refugees after arrival in this country. The CDC screened 605 children under the age of 5 for weight, height and age and compared the findings with a control population of Asian descent already residing in this country.[41] Malnutrition was considered significant when anthropomorphic measurements were greater than 2 standard deviations below the mean of a reference population obtained from the National Center for Health Statistics.[46] Evidence for acute malnutrition, suggested by decreased weight for height, was found in 3 percent of refugees and 1 percent of the Asian control population. In children under 2 years of age, however, a 6-percent incidence was noted in refugees. A low height for age, suggestive of chronic malnutrition, was found in 38 percent of refugees but only 9 percent of the control population.

Vaccinations

Because of absent preventive health care few refugees have been adequately vaccinated by US standards. In January 1980, however, an immunization program for refugees was begun in Southeast Asian transit centers.[47] After arrival in the US immunization records should be reviewed and the vaccine series recommended for each age group should be completed.[1] This schedule is shown in Table 6.

Psychiatric and Social Problems

Given the cultural changes encountered by refugees arriving in this country and their experience during recent years, a substantial number of psychiatric problems could be anticipated. The prevalence of such disorders is unknown, but their existence is well documented.[48,49] A study of 194 refugees revealed a 10-percent incidence of psychiatric problems including psychosis, depression, tension and anxiety.[2]

Emphasis must also be placed on cultural differences between Indochinese refugees. It must be remembered that these persons represent a multitude of ethnic origins including Vietnamese, Laotians and Kampucheans. There exist major differences in language, religion, education, employment, social and family life and customs. As well, there are differences in attitude toward their traditional approaches and Western approaches to medicine.[50,51]

Conclusions

Several medical problems have been reported in Southeast Asian refugees during recent years. Infections are a significant cause of morbidity and include tuberculosis, intestinal parasites, hepatitis carriers and malaria. Anemia is common, often

due to iron deficiency and hemoglobin disorders. Acute malnutrition does not appear to be a major problem except in young children, but evidence suggests chronic malnutrition may be widespread. Psychiatric and cultural problems exist and may increase.

Based on these findings several recommendations can be made for the medical evaluation of Indochinese refugees. All persons should have a complete history and physical examination with close attention paid to nutritional status and possible psychiatric problems. Routine laboratory studies should include complete blood count (CBC) with differential, screening of stool for ova and parasites, and screening for HBsAg. Tuberculosis status should be reevaluated and a full set of immunizations based on the refugee's age should be started.

REFERENCES

1. Health status of Indochinese refugees. Morbidity Mortality Weekly Rep 28:385-398, 1979
2. Erickson RV, Hoang GN: Health problems among Indochinese refugees. Am J Public Health 70:1003-1006, 1980
3. Dean AG: Suggestions for medical screening of Southeast Asian refugees. Minn Med 62:753-754, 1979
4. Pettersen GR, Noot AE, Dean AG, et al: Health screening of Indochinese refugees. Minn Med 63:91-93, 1980
5. Health screening of resettled Indochinese refugees—Washington, DC, Utah. Morbidity Mortality Weekly Rep 29:4-11, 1980
6. Demographic Statistics by Migration and Refugee Services. Washington, DC, United States Catholic Conference, 1981
7. Smilkstein G: Refugees in Thailand and short term medical aid. JAMA 245:1052-1054, 1981
8. Dahlberg K: Medical care of Cambodian refugees. JAMA 243:1062-1065, 1980
9. Health status of Kampuchean refugees—Sakaeo, Thailand. Morbidity Mortality Weekly Rep 28:545-546, 1979
10. Glass R, Nieburg P, Cates W, et al: Rapid assessment of health status and preventive medicine needs of newly arrived Kampuchean refugees, Sa Kaeo, Thailand. Lancet 1:868-872, 1980
11. Health status of Kampuchean refugees—Khao I-Dang. Morbidity Mortality Weekly Rep 28:569-570, 1979
12. Follow-up on the health status of Kampuchean refugees—Thailand, November 1979-February 1980. Morbidity Mortality Weekly Rep 29:218-225, 1980
13. Goodman R, Dondero TJ, Schultz MG, et al: Indochinese refugees and infectious disease. Ann Intern Med 93:375, 1980
14. Tuberculosis among Indochinese refugees. Morbidity Mortality Weekly Rep 29:383-390, 573, 1980
15. Farer LS: Mycobacterium tuberculosis: Bacteriology, epidemiology, and treatment, *In* Mandell GL, Douglas RG, Bennett JE (Eds): Principles and Practices of Infectious Diseases, New York, John Wiley & Sons, 1979, pp 1905-1916
16. Cantrell RW, Jensen JN, Reid D: Diagnosis and management of tuberculous cervical adenitis. Arch Otolaryngol 101:53-57, 1975
17. Primary resistance to antituberculosis drugs—United States. Morbidity Mortality Weekly Rep 29:345-346, 1980
18. Sanford JP: Pseudomonas species (including melioidosis and glanders), *In* Mandell GL, Douglas RG, Bennett JE (Eds): Principles and Practices of Infectious Diseases. New York, John Wiley & Sons, 1979, pp 1720-1726
19. Paragonimiasis in Hmong refugees—Minnesota. Morbidity Mortality Weekly Rep 30:176-182, 1981
20. Malaria—United States, 1980. Morbidity Mortality Weekly Rep 29:285-286, 413-415, 1980
21. The importation of malaria in California Indochinese refugees. Calif Morbidity #10, Mar 14, 1980
22. Wyler DJ, Miller LH: *Plasmodium* species (malaria), *In* Mandell GL, Douglas RG, Bennett JE (Eds): Principles and Practices of Infectious Diseases. New York, John Wiley & Sons, 1979, pp 2097-2110
23. Drugs for Parasitic Infections. Med Lett Drugs Ther 21. 105-112, 1979
24. Krotoski WA: Frequency of relapse and primaquine resistance in Southeast Asian vivax malaria. N Engl J Med 303:587, 1980
25. *Plasmodium falciparum* malaria contracted in Thailand resistant of chloroquine and sulfonamide-pyrimethamine. Morbidity Mortality Weekly Rep 29:493-495, 1980
26. Jones MJ, Thompson JN, Brewer NS: Infectious diseases of Indochinese refugees. Mayo Clin Proc 55:482-488, 1980
27. Temcharoen P, Viboolyavatana J, Wanaratana L: A survey on intestinal parasitic infections in Laotian refugees at Ubon Province, Northeastern Thailand, with special reference to schistosomiasis. Southeast Asian J Trop Med Public Health 10:552-555, Dec 1979
28. Wiesenthal AM, Nickels MK, Hahimoto G, et al: Intestinal parasites in Southeast Asian refugees. JAMA 244:2543-2544, 1980
29. Parasitic diseases screening of Southeast Asian refugees. Calif Morbidity #13, Apr 4, 1980
30. Lindes C: Intestinal parasites in Laotian refugees. J Fam Pract 9:819-822, 1979
31. Arrekul S: The nature and course of hookworm anemia. J Med Assoc Thai 63:177-179, 1980
32. Keystone JS, Murdoch JK: Mebendazole. Ann Intern Med 91:582-586, 1979
33. Mahmoud AF: Intestinal nematodes (roundworms), *In* Mandell GL, Douglas RG, Bennett JE (Eds): Principles and Practices of Infectious Diseases. New York, John Wiley & Sons, 1979, pp 2157-2164
34. Viral hepatitis type B, tuberculosis, and dental care of Indochinese refugees. Morbidity Mortality Weekly Rep 29:1-3, 1980
35. Phillips SJ, Pearson RJ: Dealing with Vietnamese refugees. Br Med J 282:525-527, 613-616, 1981
36. Follow-up on cholera in Indochinese refugees in the United States—California, Pennsylvania. Morbidity Mortality Weekly Rep 29:239, 1980
37. International importation of measles—New Mexico. Morbidity Mortality Weekly Rep 28:105-106, 1979
38. Diphtheria in Indochinese refugees from Thailand. Morbidity Mortality Weekly Rep 28:509-546, 1979
39. Acute hemorrhagic conjunctivitis in refugees—United States. Morbidity Mortality Weekly Rep 29:445-451, 1980
40. State Department of Health: Multiply resistant *Hemophilus influenzae* type B in Thailand. Calif Morbidity #2, Jan 23, 1981
41. Nutritional status of Southeast Asian refugee children. Morbidity Mortality Weekly Rep 29:477-479, 1980
42. Pornpatkul M, Bumrungtrakul P, Surapruk P, et al: The incidence of thalassemias and hemoglobin E in Vietnamese. Southeast Asian J Trop Med Public Health 11:142-143, Mar 1980
43. Sicard D, Kaplan JC, Labie D: Hemoglobinopathies and G-6-PD deficiency in Laos. Lancet 1:571-572, 1978
44. Wasi P, Pootrakul S, Pootrakul P, et al: Thalassemia in Thailand. Ann NY Acad Sci 344:352-362, 1980
45. Flatz G: Hemoglobin E: Distribution and population dynamics. Humangenetik 3:189-234, 1967
46. Jelliffee DB: The Assessment of the Nutritional Status of the Community. Geneva, World Health Organization, 1966, pp 176-200
47. Immunization program for Indochinese refugees. Morbidity Mortality Weekly Rep 29:38-39, 1980
48. Lin KM, Tazuma LC, Masuda M: Adaptational problems of Vietnamese refugees—I. Health and mental health status. Arch Gen Psychiatry 36:955-961, Aug 1979
49. Masuda M, Lin KM, Tazuma L: Adaptation problems of Vietnamese refugees—II. Life changes and perception of life events. Arch Gen Psychiatry 37:447-450, Apr 1980
50. Olness K: Cultural aspects in working with Lao refugees. Minn Med 62:871-874, Dec 1979
51. Kinzie JD, Tran KA, Breckenridge A, et al: An Indochinese refugee psychiatric clinic—Culturally accepted treatment approaches. Am J Psychiatry 137:1429-1432, 1980

Important Advances in Clinical Medicine

Epitomes of Progress — Preventive Medicine and Public Health

The Scientific Board of the California Medical Association presents the following inventory of items of progress in preventive medicine and public health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in preventive medicine and public health that have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Rubella Vaccine and Congenital Rubella Syndrome Prevention

In 1979 a new live-virus rubella vaccine, derived from the RA 27/3 virus strain produced in human diploid cell culture, replaced the HPV-77:DE-5 vaccine as the only commercially available rubella vaccine in the United States. (The Cendehill and HPV-77:DK-12 vaccines were withdrawn from use earlier in the 1970's.) The serum and secretory antibody response to immunization with RA 27/3 vaccine more closely resembles that following wild virus infection than does the response to HPV-77:DE-5 vaccine. The prospect that RA 27/3 vaccine confers lifelong immunity appears very good; the probability for HPV-77:DE-5 vaccine, while good, may be slightly lower.

Sufficient field studies have shown that those immunized with rubella vaccine do not spread their live-virus infection to others; thus, persons who are household contacts of pregnant women can be immunized. Transient mild arthralgia and, rarely, transient arthritis may result from immunization in persons susceptible to rubella.

While rubella vaccine viruses can cross the placenta, the risk of teratogenesis from inadvertent immunization of a pregnant woman is low or nonexistent. It has been reported that 94 susceptible women who received HPV-77:DE-5 or Cendehill vaccine just before conception or during the first trimester of pregnancy have been delivered of normal babies. Although a much smaller number of cases (17) has been documented for RA 27/3 vaccine, there has been no proved case of congenital rubella syndrome (CRS) resulting from immunization. Nonetheless, pregnant women should not be given rubella vaccine. The US Public Health Service recommends that women of childbearing age be asked if they are pregnant before being vaccinated. If they say "no," they should be advised of the theoretical risk, instructed to avoid pregnancy for the next three months and then immunized. When time and cost are not prohibitive, women of childbearing age can be tested serologically for susceptibility before immunization, but this procedure should not be allowed to interfere with effective immunization programs.

In the United States the goal has been universal

immunization of all children shortly after one year of age, thereby eliminating the major reservoir of infection. In the prevaccine era, immunity to rubella rose gradually through the first two decades of life, reaching about 85 percent in persons 20 years or older. Since the vaccine was introduced in 1969, more than 90 million doses have been distributed in this country. According to a recent California survey, by age 5 nearly 80 percent of children are seropositive, with little increase in prevalence of immunity among older children and young adults.

The effect of this reduction in the reservoir of susceptible persons has been (1) the elimination of periodic major rubella epidemics with subsequent major increases in CRS births such as that which occurred in 1964 to 1965 and (2) a general reduction in interepidemic rubella incidence, which is more pronounced in younger children than in teenagers and young adults. The interepidemic incidence of CRS appears to have decreased, although diagnostic and reporting inaccuracies make this observation tenuous.

In the United States, small-to-moderate outbreaks of rubella continue to occur among teenagers and young adults, where the risk of exposure to susceptible pregnant women is rather high. Two measures can alleviate this situation. First, since 1980 all 50 states have required rubella immunization of children entering school. If this requirement is enforced, more than 90 percent of the population should be immune by five years of age. However, because in most states this legal requirement is limited to elementary school entry because of concerns about immunizing postpubertal females, an impact on disease incidence among teenagers and young adults may not occur for at least ten years. Second, it is widely recommended that increased emphasis be placed on immunization of susceptible females of childbearing age, especially at several "checkpoints": premaritally, at college and military service entry, in family planning clinics, at entry to employment in hospitals and clinics, and immediately after childbirth (this last measure poses no known serious risk to breast-fed infants). Also, some investigators have urged a policy of immunizing girls just before puberty, including those previously immunized, because available data indicate that reimmunization of seronegative vaccinees with RA 27/3 vaccine is effective. The need for such a reimmunization policy for rubella is still being debated.

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REFERENCES

Krugman S: Rubella immunization: Present status and future perspectives. Pediatrics 65:1174-1176, Jun 1980

Balfour HH Jr: Rubella reimmunization now. Am J Dis Child 133:1231-1233, Dec 1979

Rubella surveillance, January 1976-December 1978 (HHS Publ No. [CDC] 80-8023). Atlanta, Centers for Disease Control, May 1980

Contamination of Drinking Water by Organic Chemicals

TRICHLOROETHYLENE (TCE) and dibromochloropropane (DBCP) were widely used chemicals in industry (TCE) and agriculture (DBCP). DBCP is no longer used as an agricultural nematocide, but TCE is still used as an industrial degreasing agent. Both of the chemical compounds have been found in significant concentrations in drinking water supplies derived from groundwater sources.

Until it was banned for use in California in 1977, DBCP was used extensively for the control of nematodes. In 1961 DBCP was shown to cause sterility and testicular atrophy in animals; in 1973 it was shown to be a carcinogen, and in 1977 it was shown to be mutagenic in the Ames test. It is now apparent that agricultural application of DBCP has resulted in the contamination of groundwater supplies and, while the investigative work continues, the contamination levels are increasing and new areas are being discovered. It is estimated that in California more than 250,000 people have been drinking water with from 0.05 to 60 parts per billion DBCP for an unknown period of time.

TCE is thought to be much less dangerous and not as active as DBCP, but the area and the apparent levels of contamination are much greater. In the past TCE was regulated primarily as an industrial health hazard; however, with the discovery of groundwater contamination in the range of one to 1,000 parts per billion, the possibility of exposure from drinking water must be considered. As with DBCP, industrial use and subsequent disposal of TCE has resulted in the contamination of drinking water supplies derived from groundwater. Likely contamination sites include areas near old industrial landfills, aerospace industrial areas, and major military and civilian airports.

The US Environmental Protection Agency (EPA) considers TCE to be a potential human carcinogen and recommends no exposure by humans to TCE. They further suggest that because a zero concentration in drinking water may be infeasible or impossible, an appropriate cancer risk level should be developed to aid in minimizing exposure and estimating the additional incidence

of cancer that may result in an exposed population.

Investigation of the extent and impact of groundwater contamination continues, and appropriate criteria for use of DBCP and TCE are expected shortly. An epidemiological survey of some DBCP-contaminated areas is under way so that adverse health effects can be determined.

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REFERENCES

Ames BN: Environmental chemicals causing cancer and genetic birth defects. Berkeley, Institute of Governmental Studies, University of California, 1978

Page T, Harris R, Bruser J: Removal of carcinogens from drinking water—A cost-benefit analysis. Pasadena, California Institute of Technology, Social Science Working Paper 230, Jan 1979

Ambient Water Quality Criteria for Trichloroethylene. USEPA, Oct 1980 EPA 440/5-80-077

Diphtheria and Tetanus Immunization for Older Adults

ABOUT 100 CASES each of tetanus and diphtheria are reported each year in the United States. The majority of tetanus cases occur in middle-aged and elderly adults and follow injuries sustained around the home and garden. Frequently the wound is so minor that medical treatment is not sought before tetanus develops. The case-fatality rate for tetanus approaches 40 percent. While most diphtheria cases occur in children, there are indications of increasing frequency in adults, especially among vagrant men. The diphtheria fatality rate is about 10 percent.

Persons born before the early 1940's, when tetanus and diphtheria toxoids came into widespread use, are likely to be inadequately immunized against these diseases. Serological surveys of elderly adults show that less than 50 percent, and in some instances as few as 30 percent, have adequate immunity to tetanus. For diphtheria the comparable figure may be as low as 20 percent.

The US Public Health Service recommends that all unimmunized persons 7 years old and older have a primary immunization series with adult-type tetanus-diphtheria toxoids (Td) consisting of three doses, the first two given four to eight weeks apart and the third given 6 to 12 months after the second. All adults should, but commonly do not, receive booster doses of Td every ten years for life. The tetanus toxoid component of Td is similar to that in pediatric diphtheria-pertussis-tetanus vaccine; however, only 10 percent to 25 percent as much diphtheria toxoid is present in the adult preparation. Severe local reactions to Td occur in 1 percent to 2 percent of adults vaccinated, and serious systemic reactions are extremely rare. Many of the severe reactions are the result of overimmunization.

Because elderly adults are often inadequately protected against tetanus and diphtheria, adults should be advised to obtain a Td booster every ten years. Middle-aged and elderly patients should be asked routinely whether they have received a tetanus-diphtheria booster during the preceding ten years. If the answer is uncertain or negative, a booster dose of Td should be given.

Adults who have received wounds should be treated as follows: If the patient has a history of two or fewer tetanus toxoid doses or an uncertain history, a Td booster dose should be given, with follow-up doses given later to bring the lifetime total to three. If the patient has a history of receiving at least three previous doses of tetanus toxoid, appropriate management depends on the nature of the wound. With a clean, minor wound, no Td booster is needed unless more than ten years have elapsed since the last dose; if the wound is more serious or involves a puncture, a Td booster should be given if more than five years have elapsed since the last dose. The use of Td, rather than single-antigen tetanus toxoid, is advised so that this dose can serve as a routine diphtheria booster as well.

Persons with only one previous dose of tetanus toxoid or an uncertain immunization history who have serious wounds (for example, deep puncture wounds, wounds with devitalized tissue, deep wounds contaminated with dirt) should be considered for passive prophylaxis with tetanus immune globulin and possibly penicillin chemoprophylaxis in addition to the necessary Td doses to complete a primary series.

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REFERENCES

Thorley JD, Holmes RK, Sanford JP: Tetanus and diphtheria antitoxin levels following a hospital-based adult immunization program. Am J Epidemiol 101:438-443, May 1975

Crossley K, Irvine P, Warren JB, et al: Tetanus and diphtheria immunity in urban Minnesota adults. JAMA 242:2298-2300, Nov 23, 1979

The Effect of Alcohol on Unborn Babies

IN 1963 Jones and associates described a specific pattern of malformation, called the fetal alcohol syndrome, in the offspring of alcoholic women who continued to drink during pregnancy. The principal features of the disorder include prenatal-onset growth deficiency, developmental delay and

a variety of structural defects including short palpebral fissures, a long philtrum with a thin smooth upper lip, multiple joint anomalies and cardiac defects. It has become clear that the fetal alcohol syndrome as it was initially delineated represents only a part of a more extensive problem. There are, for example, a large number of children born to women who drink either heavily or moderately during pregnancy who have features compatible with the prenatal effects of alcohol but who do not have the full-blown fetal alcohol syndrome. In a recent study from the University of Göteborg in Sweden, it was estimated that for every full-blown case of the syndrome, there is at least one child born with features compatible with the prenatal effects of alcohol who does not have the full-blown syndrome. In that prospective study, Olegard and co-workers determined that 33 percent of the offspring of alcoholic women who continued to drink heavily during pregnancy had the fetal alcohol syndrome and an additional 33 percent had features consistent with the prenatal effect of alcohol; only 33 percent of the offspring were normal. With respect to moderate alcohol consumption, Hanson and colleagues have estimated that 11 percent of the offspring of women who drink between one and two ounces of absolute alcohol a day during the first trimester of their pregnancy have features consistent with the prenatal effects of alcohol. For lesser amounts of alcohol, particularly "binge drinking" during pregnancy, no data are available.

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REFERENCES

Jones KL, Smith DW, Ulleland CN, et al: Pattern of malformation in offspring of chronic alcoholic mothers. Lancet 1:1267-1271, Jun 9, 1973

Olegard R, Sabel KG, Aronsson M, et al: Effects on the child of alcohol abuse during pregnancy—Retrospective and prospective studies. Acta Paediatr Scand (Suppl) 275:112-121, 1979

Hanson JW, Streissguth AP, Smith DW: The effects of moderate alcohol consumption during pregnancy on fetal growth and morphogenesis. J Pediatr 92:457-460, Mar 1978

Gastrointestinal Disease

SEVERAL new viral, bacterial and parasitic agents that cause gastrointestinal disease have been identified in recent years. Studies from different parts of the world have shown that up to 75 percent of acute diarrheal disease is nonbacterial. Rotavirus is the most important viral agent causing sporadic and epidemic outbreaks of diarrheal disease in those 2 years and younger. It occurs typically in winter, causing fever and diarrhea; vomiting is less prominent. Symptoms may persist for up to eight days. Parvovirus agents, including the Norwalk agent, have been found to cause diarrhea, fever and vomiting that last one to two days in children and adults. Viral gastroenteritis is treated with supportive care.

Campylobacter fetus, formerly classified as *Vibrio fetus,* has been recognized as a common cause of diarrhea in children and adults. In a recent Canadian study, *Campylobacter fetus* subspecies *jejuni* was second only to *Salmonella* as a bacterial cause of diarrhea in children. It was not recovered from stool specimens of children without symptoms. The illness was characterized by fever, abdominal pain, which may be severe, and diarrhea, which may recur. Spread throughout a household is common and pets are possible sources of this disease. No controlled studies of treatment have been reported. Isolates are usually sensitive to erythromycin, aminoglycosides, chloramphenicol and tetracycline but resistance may develop during treatment.

Yersinia enterocolitica causes gastroenteritis in children and adults. Young children often have fever, vomiting and diarrhea and leukocytes may be present in the stool. Older children may present with pseudoappendicitis, fever and abdominal pain; mesenteric lymphadenitis occurs in some cases. Adults with *Y enterocolitica* are also affected with gastroenteritis and, at times, erythema nodosum and arthritis. This infection should be considered in pseudoappendicitis, and serological test and culture are useful in establishing the diagnosis. *Y enterocolitica* has been recovered from a variety of sources including raw milk, water supplies and wild and domestic animals. Transmission can occur from other humans or from pets, and the incubation period is usually four to ten days. The efficacy of antibiotic drugs in treating active disease is unknown as is the effect on the carrier state.

Giardia lamblia, an intestinal flagellate, has been recognized as a cause of diarrhea in travelers in many parts of the world. In the past few years, outbreaks of giardiasis have occurred in the United States resulting from consumption of contaminated water supplies and person-to-person transmission. A water supply not sufficiently chlorinated may contain *Giardia* cysts. Higher chlorine concentrations or additional treatment such as coagulation flocculation, settling or filtration is needed to kill the organisms. Humans and beavers may be natural reservoirs. Persons infected with *G lamblia* may be asymptomatic car-

riers of the cysts or may have chronic diarrhea, abdominal discomfort and weight loss. The average incubation period is nine days. In the acute stage, explosive diarrhea, which is watery and foul, abdominal cramping and flatulence occur, and the diarrhea and abdominal pain may continue intermittently for months. Examination of stool specimens for ova and parasites between episodes may give negative results. Because the trophozoites are found in the upper small intestine, if repeated stool examinations are negative, duodenal intubation and aspiration may be useful in making the diagnosis. Treatment of adults with 100 mg of quinacrine three times a day for seven days give excellent results. Metronidazole therapy with 250 mg three times a day for seven days also is effective. Pediatric treatment and dosage information is provided in the first reference below.

Any outbreak of infectious diarrhea is a public health problem. Professional food handlers, medical personnel and those employed in child care should not be permitted to work while they have acute diarrhea that may be infectious. If specific bacterial infection is recognized, stool specimens should be obtained and found negative for the organism before work is resumed and local health departments should be notified.

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REFERENCES

Wolfe MS: Giardiasis. Pediatr Clin North Am 26:295-303, May 1979

Pai CH, Sorger S, Lackman L, et al: *Campylobacter* gastroenteritis in children. J Pediatr 94:589-591, Apr 1979

Side Effects of Human Diploid Cell Rabies Vaccine and Human Rabies Immune Globulin

HUMAN DIPLOID CELL RABIES VACCINE (HDCV), licensed for use in the United States since mid-1980, is an inactivated vaccine prepared from rabies virus grown in human diploid cell cultures. This product is much more immunogenic than the duck embryo rabies vaccine (DEV), the use of which declined drastically after licensure of HDCV. The manufacture of DEV ceased production in November 1981. Human rabies immune globulin (HRIG, or RIG), used to provide rapid but temporary protection, consists of antirabies gamma globulin prepared from plasma of immunized human donors.

Preexposure rabies prophylaxis, given to persons at special risk for rabies (such as veterinarians, animal control personnel and certain laboratory workers) consists of three 1-ml intramuscular injections of HDCV, the second given a week after the first and the third two to three weeks after the second. Prophylaxis for persons with a bite, scratch or saliva-to-mucous-membrane contact from a proved or suspected rabid animal consists of one intramuscular injection of HRIG, dosage based on body weight, and five intramuscular injections of HDCV, the first given the same day as HRIG and the other given 3, 7, 14 and 28 days later. Because HDCV has proved to be so highly immunogenic, collection of a serum specimen for rabies antibody testing after preexposure or postexposure prophylaxis is now recommended only for persons who received DEV or who may be immunocompromised.

Serious side effects are less frequent with HDCV than with DEV. No neuroparalytic reactions have been noted following HDCV; in about one in every 25,000 persons vaccinated with DEV transverse myelitis, encephalopathy, or cranial or peripheral neuropathy developed. One instance of Guillain-Barré syndrome (GBS) following HDCV has been reported. Isolated cases of GBS have been reported following administration of many vaccines, and it has been difficult to determine if causal relationships exist in such episodes. Local reactions, such as pain, redness or pruritus, have been reported in about 25 percent of HDCV recipients, while mild systemic reactions, such as fever, headache, nausea, diarrhea, abdominal pain, myalgia and dizziness, have been reported in 20 percent. Local or mild systemic reactions to HDCV usually can be managed with agents like aspirin and do not necessitate stopping prophylaxis. Rarely, allergic reactions ranging from hives to anaphylactic shock have been reported in HDCV recipients. If a severe allergic reaction occurs before completion of a HDCV series, the risk of rabies developing must be balanced against the risk of continuing administration of HDCV. In these situations, consultation may be obtained from state health departments and the Centers for Disease Control. Pregnancy is not a contraindication for HDCV.

Local pain and low-grade fever may occur in HRIG recipients, but more serious reactions have not been reported. Presumably, adverse reactions such as those reported rarely after use of immunoglobulin (IG; formerly called ISG or GG), including angioneurotic edema, nephrotic syndrome and anaphylaxis, could occur after HRIG. To reduce

the possibility of an immediate severe reaction to HRIG, care should be taken to administer this preparation intramuscularly and not intravenously.

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REFERENCES

Rabies prevention. Morbidity Mortality Weekly Rep 29:265-280, Jun 13, 1980

Adverse reactions to human diploid cell rabies vaccine. Morbidity Mortality Weekly Rep 29:609-610, Dec 19, 1980

Pneumococcal Vaccine

IN SPITE OF THE dramatic effect of penicillin on the clinical course of pneumococcal pneumonia—especially in young people—Austrian has recently estimated that there are between 200,000 and 1,000,000 cases of disease with 13,200 to 66,000 resultant deaths in the United States each year. In an earlier study he and Gold found the following. (1) From 20 to 25 bacteremic pneumococcal infections were seen each year for each 100 to 125 medical ward beds ("an incidence similar to that seen before the introduction of antibiotics"). (2) Almost a fifth of those patients properly treated with penicillin or other antibiotic drugs died. The fatality rate exceeded 25 percent in patients 50 years or older and in those with underlying systemic illness. (3) Sixty percent of deaths in penicillin-treated patients occurred within five days, even when treatment had been initiated in the first or second day of illness.

Pneumococcal polysaccharide vaccine, which became available in 1978, contains the capsular polysaccharides of the 14 serotypes most often associated with pneumococcal infections. Its safety and antigenicity were established in healthy young adults and in smaller groups of children and elderly persons. The duration of its protective effect has not been definitively determined. Antibody levels after vaccination occur in the same pattern as those following natural disease: after an initial peak, levels fall gradually over 6 to 12 months, then maintain a level at a third to a half the peak for at least five to eight years. To minimize reactions in persons who still have high antibody levels, revaccination should not be carried out at less than five-year intervals.

Studies of vaccine efficacy and cost-effectiveness are appearing in the literature. And although indications for its use are not yet definitive, it seems both safe and prudent to provide the protection of this vaccine to those who are at greatest risk of death from pneumococcal disease—that is, patients older than 2 years of age with underlying chronic systemic disease, especially those 50 years and older. Other groups of patients older than 2 years who may also benefit are those with sickle cell anemia, impaired splenic function or splenectomy, and children with nephrotic syndrome. (These are the same high-risk groups for whom influenza vaccine is recommended. Both vaccines may be given as they do not interfere with each other. However, they should not be mixed in the same syringe nor given at the same site.)

Pneumococcal polysaccharide vaccine should not be administered to those hypersensitive to any of the vaccine's components, to pregnant women or to children younger than 2 years old. Caution should be exercised in cases of febrile respiratory illness, in persons with severely compromised cardiac or pulmonary function in whom a systemic reaction would pose a significant risk and in patients who have had pneumococcal infections in the preceding three years.

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REFERENCES

Austrian R: Vaccines of pneumococcal capsular polysaccharides and the prevention of pneumococcal pneumonia, chap 8, *In* Beers RF Jr, Basset E (Eds): The Role of Immunological Factors in Infectious, Allergic, and Autoimmune Processes. New York, Raven Press, 1976, pp 79-89

Austrian R, Gold J: Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. Ann Intern Med 60:759-776, May 1964

Austrian R: The assessment of pneumococcal vaccine (Editorial). N Engl J Med 303:578-580, Sep 4, 1980

Hemophilus influenzae Prophylaxis

THE SECONDARY ATTACK RATE of *Hemophilus influenzae* type b meningitis is similar to that of meningococcal meningitis—that is, approximately 2 percent in children younger than 5 years old living at home and as high as 6 percent in infants younger than 1 year. A significant risk of secondary cases also exists in day-care centers for preschool children.

Clinical trials and pharmacokinetic studies suggest that the best drug for chemoprophylaxis of such secondary cases is rifampin in a single daily dose of 20 mg per kg of body weight per day for four days (the maximal dose is 600 mg per day). No liquid preparation is commercially available but the contents of a 300 mg capsule suspended in 30 ml of 85 percent sucrose is readily accepted by infants and children and produces reliable serum and salivary levels. Most studies show that this regimen is likely to eradicate *Hemophilus influenzae* type b carriage in the nasopharynx. Other antimicrobials such as ampicillin, cefaclor, sulfisoxazole and trimethoprim

sulfamethoxazole have not been successful in eradicating carriage.

The goal of such prophylactic therapy is not elimination of the carrier state but prevention of disease. There are no controlled studies showing reduction of systemic *Hemophilus influenzae* type b disease with chemoprophylaxis. A national collaborative study of this problem has just been concluded but the results are not available at this time.

Our own practice is to prescribe rifampin for contacts of a child having *Hemophilus influenzae* meningitis. We give it to all members of a household that includes another child younger than 5 years old. We also recommend that chemoprophylaxis be considered for other children and staff in day-care centers. Since the effectiveness of this regimen is not known, such prophylaxis should not be a substitute for close surveillance.

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REFERENCES

Ward JI, Fraser DW, Baraff LJ, et al: *Haemophilus influenzae* meningitis—A national study of secondary spread in household contacts. N Engl J Med 301:122-126, Jul 19, 1979

Shapiro ED, Wald ER: Efficacy of rifampin in eliminating pharyngeal carriage of *Haemophilus influenzae* type b. Pediatrics 66:5-8, Jul 1980

Gessert C, Granoff DM, Gilsdorf J: Comparison of rifampin and ampicillin in day care center contacts of *Haemophilus influenzae* type b disease. Pediatrics 66:1-4, Jul 1980

McCracken GH Jr, Ginsburg CM, Zweighaft TC, et al: Pharmacokinetics of rifampin in infants and children: Relevance to prophylaxis against *Haemophilus influenzae* type b disease. Pediatrics 66:17-21, Jul 1980

Daum RS, Glode MP, Goldmann DA, et al: Rifampin chemoprophylaxis for household contacts of patients with invasive infections due to *Haemophilus influenzae* type b. J Pediatr 98:485-491, Mar 1981

Zoonoses

A ZOONOSIS is a disease transmitted from an animal, usually a vertebrate, to humans. In most cases, the person is exposed because of occupation or avocation. In the textbook by Hubbert and coworkers, *Diseases Transmitted from Animals to Man,* more than 100 conditions are listed; however, only those commonly associated with household pets will be mentioned here.

Psittacosis, a chlamydial infection of birds (especially parakeets, parrots and pigeons), is becoming more common. In 1978, 88 percent of cases in the United States occurred in persons with occupational or hobby exposure to birds. The bird may harbor this organism for a long time and be asymptomatic; however, shedding will occur when the bird is stressed by shipping or illness. In humans, infection usually results from inhalation of the agent from desiccated droppings and often presents as an acute, febrile illness characterized by headache, nonproductive cough, anorexia and change in bowel habit. Pneumonia, demonstrable on x-ray studies of the chest, develops in most patients. Recovery of the agent is not routinely done, but the diagnosis may be established by showing a fourfold or greater titer increase between acute and convalescent specimens in complement fixation antibodies. The treatment of choice in adults is tetracycline, 500 mg every six hours, continued for 10 to 14 days after the patient defervesces. A public health veterinarian should be consulted about treatment of the bird since appropriate treatment varies with the species.

Toxoplasmosis, a systemic protozoan infection, may be acquired or congenital. Acquired toxoplasmosis usually results from human exposure to the oocysts, which sporulate and become infective one to five days after excretion in the feces by a cat. The cat is usually asymptomatic and may shed oocysts intermittently. Human disease may also follow consumption of inadequately cooked meat. The spectrum of disease in humans ranges from asymptomatic infection to acute febrile illness characterized by lymphadenopathy. In a recent outbreak, fever, lymphadenopathy, headache and myalgia developed in most of the symptomatic persons. Of these, 25 sought medical attention but only 12 percent were diagnosed as having toxoplasmosis. Diagnosis may be established by determining serum toxoplasma antibody seroconversion by indirect fluorescent-antibody test or demonstrating a specific toxoplasma IgM antibody titer of 1:16 or greater. A primary infection of women during early pregnancy may lead to death of the fetus. Infection later in pregnancy may cause chorioretinitis and brain damage to the fetus. Newborn infants and symptomatic adults who are not pregnant should be treated with sulfadiazine and pyramethamine. The threat of exposure can be reduced if cat litter is disposed of daily by a person who is not pregnant.

Dogs and cats, particularly when they are young, may transmit many other agents to their owners, including *Yersinia enterocolitica, Giardia lamblia* and *Campylobacter fetus*—all of which cause diarrhea. *Pasturella novicida,* cat scratch fever, *Toxocara canis* and *T cati* (the last two cause visceral larva migrans) are common in pets. Children acquire these infections by eating dirt containing the eggs. Infection can be prevented by periodic deworming of household dogs and discouraging pica in children.

Some zoonoses, such as animal ringworm, are

a nuisance to humans; others, such as leptospirosis may be life threatening. Thus, pediatric and adult histories should include questions concerning exposure to animals at work, at home or through recreational activities, such as camping, to speed accurate diagnosis of the illness.

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REFERENCE

Teutsch SM, Juranek DD, Sulzer A, et al: Epidemic toxoplasmosis associated with infected cats. N Engl J Med 300:695-699, Mar 29, 1979

The Hazard in Consuming Raw Milk

A RECENT EDITORIAL in *The Lancet* noted that Q fever, paratyphoid fever and gastrointestinal infections such as *Campylobacter* sp, enteropathogenic *Escherichia coli* and *Salmonella* sp can be delivered straight to your door—in raw milk. Tuberculosis and brucellosis from raw milk were major public health problems in the past but have come under excellent control in US dairy herds. However, the recurring outbreaks of *Campylobacter* infection and salmonellosis associated with raw milk consumption in the western United States and elsewhere are disturbing. In early 1981 large outbreaks of *Campylobacter* infection associated with raw milk were reported from Arizona, Kansas and Oregon and outbreaks of *Salmonella* infection were reported from Montana and Washington State.

No type or grade of raw milk including "certified" raw milk is safe from these infections. Salmonellae have been recovered repeatedly from California-produced raw milk, including certified milk, and salmonella outbreaks have occurred in California in association with certified milk. Milk that is "certified" is not certified to be free of pathogens. Rather, certification is a copyrighted designation indicating the milk was produced according to methods and standards specified by the American Association of Medical Milk Commissions, Inc.—methods that have repeatedly failed to prevent contamination with human pathogens.

The most important route by which salmonellae get into milk is through bovine fecal contamination. Yet, salmonellae have been isolated from the udders of cows both with and without mastitis, even when there was no concurrent intestinal infection (as evidenced by positive fecal culture). Thus, milk may become contaminated with salmonellae without exposure to feces or other exogenous sources of contamination.

Salmonella contamination of raw milk may be intermittent and low-grade; and contamination need not be uniformly distributed in a day's production: when the Food and Drug Administration cultured certified raw milk in California in February 1981 in the largest one-day survey to date, they found 20 percent of the containers (4 of 20 half-gallon cartons) produced and bottled by one dairy on the same day to be contaminated with salmonellae.

The route by which *Campylobacter* contaminates milk has not been precisely defined. The probable mechanism is direct fecal contamination since 60 percent of healthy cattle excrete *Campylobacter* in their feces, and *Campylobacter* mastitis has not yet been shown to occur naturally.

Present technology *cannot* prevent or eradicate *Salmonella* and *Campylobacter* infection in milking herds, nor can it prevent contamination of milk produced by such infected cattle. Because occasional fecal contamination occurs during the milking process despite the best efforts of dairies to prevent it, the result is human infection and disease unless milk is pasteurized.

Salmonella and *Campylobacter* diseases in humans are generally not serious but in persons with compromised health (particularly those with malignant conditions and those immunosuppressed by disease or therapy), these infections may be serious. In immunocompromised persons invasive disease with bacteremia, sepsis and widespread dissemination tends to develop; death is not uncommon. Yet "health foods" such as raw milk are sometimes recommended as an adjunct to conventional (and unconventional) therapy for these immunocompromised persons.

Contamination of raw milk has been known since antiquity: a cuneiform tablet from ancient Sumer in lower Mesopotamia written about 5,000 years ago carried the ancient milkers' complaint that if the gods really wanted people to have "clean" milk they would have ". . . placed the udders on the forepart of the cows." But people can have "clean" (safe) milk—through pasteurization. This process not only kills milkborne pathogens that are infective at low doses but also protects consumers from pathogens (infective at only high doses) that could multiply to great numbers if milk contaminated with pathogens were not continuously refrigerated.

Several professional groups, including the *American Academy of Pediatrics,* the *Conference of State and Territorial Epidemiologists,* the *American Veterinary Medical Association* (AVMA),

the *US Animal Health Association* and the *National Association of State Public Health Veterinarians* have adopted policy statements that milk and milk products for human consumption be pasteurized. In some 20 states where the sale of raw milk is legal, the AVMA has recommended that raw milk carry a warning label: "Not pasteurized and may contain organisms that cause human disease." Consumers should know the risks involved.

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REFERENCES

Hazards of untreated milk. Lancet 1:705, Mar 28, 1981

Werner SB, Humphrey GL, Kamei I: Association between raw milk and human *Salmonella dublin* infection. Br Med J 2:238-241, Jul 28, 1979

Taylor PR, Weinstein WM, Bryner JH: *Campylobacter fetus* infection in human subjects: Association with raw milk. Am J Med 66:779-783, May 1979

Jensen LB: Poisoning Misadventures—Narrative Excerpts on Food-Borne Diseases and Poisoning for the Physician, Microbiologist, Attorney, and Nutritionist. Springfield, Illinois, Charles C Thomas, 1970

Current Testing of the Neonate

MANDATORY SCREENING of newborns for phenylketonuria (PKU) has been a public health program in all but a few states since the mid-1960's. In recent years more than half the states have expanded this preventive program to include hypothyroid and galactosemia screening.

Such programs function best when they are organized at the state level and include parental and physician education, centralized automated testing, regionalized follow-up services, access to expert diagnostic consultation and specialized referral centers for treatment.

These mass screening programs are intended to assist and supplement the clinical skills and judgments of physicians and not to replace them. It is important to pursue appropriate diagnostic tests immediately whenever history, symptoms or signs raise a suspicion of one of these diseases. Physicians should not wait for mass screening tests to make or rule out the diagnosis because there is the remote possibility of false negatives and there are always more false positives than true cases. As with any laboratory test, judgment must be used in deciding whether to repeat the test where there have been borderline results.

PKU screening has evolved from the semiquantitative microbiological inhibition assay developed by Dr. Robert Guthrie to a precise quantitative automated fluorometric analysis. This permits the selection of cutoff levels to minimize the false positives while still keeping an acceptably low rate of false negatives. The timing of the test has become an important issue because increasing numbers of infants are being discharged earlier than in the past. Prospective and retrospective studies of the screening results of classic cases sampled over the first four days of life support the concept that such testing has an acceptably low rate of missed cases even though slightly higher than later (after the fourth day) testing. Protein ingestion accentuates positive results but is not critical at the cutoff selected (4.3 mg per dl).

Additional screening information has uncovered a variety of hyperphenylalanemic syndromes in addition to classic PKU. These include transient to persistent hyperphenylalanemia with levels below 20 mg per dl, dihydropteridine reductase or biopterin deficiency, and transient PKU with acquired ability to metabolize phenylalanine. Because information on the diagnosis and treatment of these conditions is constantly growing, referral to or consultation with a metabolic center is highly desirable when there are positive results.

Hypothyroid screening is a two-stage process using thyroxine (T_4) as a prescreen. The lowest 5 percent of T_4 results are scheduled for thyroid-stimulating hormone (TSH) analysis. The absolute normal range of serum T_4 varies with an infant's age and can be transiently lowered by stressful conditions such as serious infection or respiratory distress. The 5 percent cutoff, therefore, will include many values that are physiologically normal or explainable by conditions other than hypothyroidism. The TSH analysis is the definitive screening test but by itself is not diagnostic. Most screening programs report even low level elevations of TSH (25 μU per ml) as positive. This might represent ectopic thyroid tissue that produces limited amounts of T_4 and could cease production at any time. Therefore repeat quantitative serum TSH, and, if available, iodine 123 scans are indicated. Hyperthyrotropemia and transient hypothyroidism must also be considered before instituting thyroxine therapy.

The statistically low T_4 levels with normal (less than 25 μU per ml) TSH results have also caused some concern. Most of these occur in premature infants, or indicate benign deficiency of thyroxine binding globulin. Secondary hypothyroidism is very rare (1 case per 100,000 births). Only one case of primary hypothyroidism has been discovered in a group of almost 5,000 infants with these results. Again it is strongly recommended

that any questionable screening results be reviewed with a pediatric endocrinologist.

Finally, galactosemia screening has been improved by quantitating and automating the galactose-l-phosphate uridyl transferase assay of Beutler. This has reduced the number of false positives although it will detect some of the low levels seen in variants such as the Duarte-galactosemia mixed heterozygote. Use of a blood galactose screen to resolve some equivocal results without collection of a venous specimen is being evaluated and also has the potential to pick up galactokinase, a clinically significant condition, and 4-epimerase, a benign condition. The safest course when suspicious results are obtained is to switch to a galactose-free formula for the infant and obtain consultation from a metabolic center. It should be remembered that after galactose exposure the urine may contain reducing substances when either transferase or kinase deficiency is present. Eyes should be examined carefully for diffuse metabolic cataracts and liver function should be checked whenever disorder of galactose metabolism is suspected. Because this is an enzyme test for which an infant's red cells are needed, test results may be obscured if a transfusion has been done.

Other hereditary metabolic conditions have been proposed and are being evaluated but have not met all the criteria necessary for inclusion in a statewide mandatory screening program.

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REFERENCES

Mamunes P: Neonatal screening tests. Pediatr Clin North Am 27:733-751, Nov 1980

Meryash DL, Levy HL, Guthrie R, et al: Prospective study of early neonatal screening for phenylketonuria. N Engl J Med 304: 294-296, Jan 29, 1981

Fisher DA, Klein AH: Thyroid development and disorders of thyroid function in the newborn. N Engl J Med 304:702-712, Mar 19, 1981

Hadeed AJ, Klein AH, Fisher DA: Significance of transient postnatal hypothyroxinemia in premature infants with and without RDS. Pediatrics 68:494-498, Oct 1981

Control of Hepatitis A in Day-Care Centers

TRANSMISSION OF HEPATITIS A in day-care centers is an increasingly recognized problem. Outbreaks have been reported in at least 17 states in the past three years. Nationwide, between 9 percent and 12 percent of hepatitis type A or hepatitis, type unspecified, is estimated to be related to day-care centers, and in some areas has approached 40 percent.

Three characteristics are common to hepatitis outbreaks related to day-care: (1) hepatitis in children of day-care age is usually asymptomatic; (2) other members in the children's households are often infected as a consequence of spread within a center and generally constitute the majority of recognized cases; and (3) diapered children 2 years or younger are most likely to transmit infection to household contacts; children 4 years and older rarely spread infection beyond the center. Thus, center directors, parents, physicians and public health authorities should recognize that infection in families of children attending the center may indicate asymptomatic spread among children at the center.

Several factors may increase the risk of a hepatitis outbreak at a day-care center: (1) a large center population (more than 20 children), (2) long hours of operation (more than nine hours per day) and (3) the presence of diapered children under the age of 2 years. The last factor is the primary one in facilitating transmission of hepatitis A. In one study, after an index case occurred in a child or center employee, 70 percent of those centers enrolling children younger than 2 years had outbreaks; by contrast, 10 percent of the centers enrolling only children aged 2 years or older had outbreaks.

Prevention and control of hepatitis in day-care centers should focus on diapered infants and toddlers 2 years or younger. Maintenance of appropriate hygienic standards, particularly scrupulous handwashing by staff and of young children who cannot adequately wash themselves, must be emphasized. Surfaces on which diapers are changed should be impermeable and should be cleaned and disinfected with an appropriate germicide. The Centers for Disease Control recommend a 1:32 dilution (½ cup per gallon) of household bleach in tap water, prepared daily and dispensed in spray bottles. Accessory items, such as cans of baby powder and jars of vaseline or lotion, should also be disinfected each day, as they can be inadvertently contaminated with feces during a diaper change. Food must not be prepared or served on surfaces where diapers are changed. Health departments should provide periodic inservice training of day-care center staff for the prevention of hepatitis A and other fecally transmitted infections, for example, giardiasis and shigellosis.

Day-care-related outbreaks of hepatitis can be controlled in several ways. First, centers may suspend admission of new children or require them to receive prophylactic immune globulin (formerly called "immune serum globulin" or

"gamma globulin") before entering. The efficacy of administering immune globulin to all children and employees at day-care centers in outbreaks is being evaluated. However, it appears that the presence of even one case in a child or employee of a center that has children under the age of 2 is an indication for administering immune globulin to all center children and employees. For six weeks following the last case, any child newly admitted to the center should also receive immune globulin. When several cases are recognized simultaneously in multiple families associated with a single center, administration of immune globulin to household contacts of children 3 years or younger also should be considered. In those centers having only children older than 2 years of age, spread is less likely after an index infection, and immune globulin usually is indicated only for center staff, age-group contacts at the center and for household contacts of the infected child.

Second, outbreaks can be further controlled by preventing the spread of disease to other centers. Centers where infection has occurred should not be closed and parents should be urged not to transfer their children—and thus, infection—to other centers.

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REFERENCES

Storch G, McFarland LM, Kelso K, et al: Viral hepatitis associated with day-care centers. JAMA 242:1514-1518, Oct 5, 1979

Hadler SC, Webster HM, Erben JJ, et al: Hepatitis A in day-care centers: A community-wide assessment. N Engl J Med 302: 1222-1227, May 29, 1980

Hepatitis Surveillance Report No. 45. Atlanta, Centers for Disease Control, May 1980

Hepatitis A outbreak in a day-care center. Morbidity Mortality Weekly Rep 29:565-567, Nov 28, 1980

Medical Problems in Homosexual Men

SOME URBAN AREAS have large numbers of homosexual residents and several infectious diseases are reportedly much higher among these special groups than in the overall urban population. As a group, homosexual men tend to be more sexually active with multiple partners than their heterosexual peers. This greater degree of sexual activity is reflected in a higher incidence rate of sexually transmitted diseases, such as syphilis, gonorrhea, nongonorrheal urethritis, herpes and acuminate warts. Asymptomatic carriers of rectal gonorrhea and rectal herpes are an important reservoir of infection.

Following syphilis and gonorrhea, shigellosis, amebiasis, giardiasis and hepatitis A are the most frequently reported infectious diseases among homosexual men. Formerly, it was believed that these infections were usually transmitted by ingestion of fecally contaminated food or water. Epidemiologic study now suggests that multiple sexual contacts of oral-anal and orogenital character are a major means of transmitting these enteric infections. While these modes of sexual interplay are not exclusively homosexual practices, the incidence rates of these enteric diseases reported among men 20 to 40 years old are six to ten times greater than those reported in women or men in any other age groups, and 60 percent to 70 percent of these reported patients are homosexual men. A small, unmeasurable percentage of patients with enteric infection remain asymptomatic carriers of the pathogens after recovery.

Special precautions are required to protect the public from infection transmitted by the 5 percent to 10 percent of patients with enteric disease who work as food handlers, bartenders, attendants in medical care facilities, and as teachers and aides in day-care centers for infants and young children.

Hepatitis B is also endemic, as shown by an almost 70 percent carrier rate of the antibody in selected groups of homosexual men. The infection may be transmitted by infected serum from minor abrasions into small breaks in anal or rectal mucosa. Saliva and semen also carry the hepatitis B antigen.

A new entity has just been added to the catalogue of medical conditions listed above. As of November 1981 more than 100 cases of *Pneumocystis carinii* pneumonia and Kaposi sarcomatosis were already known, having developed in various combinations in young homosexual men in United States cities on both coasts. Of the cases 24 were then known in the San Francisco Bay Area (eight of the patients had died) and more were reported from the Los Angeles area. Kaposi sarcoma and *Pneumocystis* pneumonia were proving rapidly fatal to some patients in this presumably fairly healthy population. In contrast, the malignant condition was formerly reported as taking a rather indolent course in very elderly persons in Africa, or as developing in patients elsewhere who were receiving immunosuppressive therapy for other medical conditions. Units from the Centers for Disease Control are cooperating in epidemiologic studies with local public health departments and private physicians. Suspected interrelationship—possibly on a genetic level—of Epstein-Barr virus, cytomegalovirus and perhaps

some local peculiarities of the male homosexual life-style make this problem the epidemiologic challenge of the year.

Special surgical problems among homosexual men may include anal or rectal abrasions, ulcers or fissures; surgical emergencies due to rectal perforations or impaction of foreign bodies; and internal acuminate warts. Surgeons may also need to differentiate (before surgical intervention) between rectal carcinoma and infections in either traumatic, amebic or herpetic ulcerations of the rectal mucosa.

Physicians should be aware that patients with emotional problems related to their homosexuality may conceal their life-style and thereby give a misleading history of their medical problems. Physicians also should be aware of possible subconscious hostility toward male homosexuality, which may impede effective diagnosis and treatment of patients' medical problems.

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REFERENCES

Dritz SK, Goldsmith RS: Sexually transmissible protozoal, bacterial and viral enteric infections. Compr Ther 6:34-40, Jan 1980

Owen RL, Dritz SK, Wibbelsman CJ: Venereal aspects of gastroenterology (Medical Staff Conference—University of California, San Francisco). West J Med 130:236-246, Mar 1979

Heathcote J, Cameron CH, Dane DS: Hepatitis-B antigen in saliva and semen. Lancet 1:71-73, Jan 19, 1974

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EDITORIALS

An Idea Whose Time Has Yet to Come

AN ARTICLE and two editorial comments appearing elsewhere in this issue express differing views concerning the education and training needed to enable a physician to perform effectively in what is being called primary care. The opinions of family medicine (also called family or general practice) and general internal medicine (to some extent including general pediatrics, obstetrics and gynecology, and even some other "primary care" specialties) are discussed. Reference also is made to the primary care being given by many specialists and subspecialists of all kinds, almost as a necessary part of their subspecialty care. One senses that these are strongly held opinions, and that it is possible we have to come to a point where no physician is adequately trained to care for the total needs of the total patient—or even most of them.

To this writer it appears that family medicine sees the family (which can be defined in various ways) as an interacting social and medical microcosm and that it is the role of a family physician to consider the ailments of a patient as these affect and are affected by this interaction. Internists see themselves more as personal physicians, that is, they tend to focus more on the patient as an individual and it is not unusual to have more than one internist caring for different persons in the same family. However, internists are also concerned with environmental and social factors as these affect their patients. And subspecialists are generally more oriented toward the disease that afflicts their patients, and are more apt to assume necessary primary care responsibilities simply as an added service to their patients.

It is obvious that there are differing views of what constitutes primary care and the services that a physician who renders primary care should be prepared to offer. As is so often the case these days, there is no clear and accepted definition of exactly what we are talking about. Historically, if one goes back far enough, all physicians were expected to be able to do everything any physician did, and this idea still persists in the all-inclusive license to practice as physicians and surgeons. But the fact is that all practicing physicians in this day and age are specialized to a greater or lesser degree. Some few have become ultimately specialized technicians who apply their specific expertise with only minimal and transient attention to the needs of the patient as a whole. This is true of many surgeons, for example, and as the technology of medicine advances there will be more of these very specialized technicians who are more or less oriented toward single diseases or procedures. This is fine, a natural outgrowth of scientific and technologic progress. But there is a comparable and growing need for care addressed to the patient as a person in interaction with his or her personal environment, and also a need for a single source of all-purpose direct care for common ailments and for competent triage services—and a need for these for all age groups. The term *primary care* appears to be used for each of these latter services, but they are not all the same.

It would seem logical, even necessary, to recognize that while each practicing physician will develop one or more special interests or specialties, most physicians in whatever specialties should have competence also to render primary care in what might be called the wholistic definition alluded to above. Just as a patient is a whole being, so should a physician offering primary care be prepared to address all the health care needs of this whole person. In this concept most physicians will need to acquire and maintain skills, albeit at a very basic level, in many specialties and subspecialties other than their own, and, in order to be competent in triage, also possess a working knowledge of the current capabilities and limitations of virtually all the specialties in medical practice. But one must be realistic and realistically one can only say that this is an idea whose time has yet to come, if indeed it ever comes at all.

—MSMW

The Lowly and the Low White Count

TIME WAS WHEN the self-dependent practitioner of medicine relied on a searching history, a probing physical examination and, if indicated, one or two simple laboratory tests to reach a tenable diagnosis of the patient's ailment. This would yield satisfactory results in the large majority of cases then, as it would even today. The laboratory tests were easily carried out in the physician's office—a urine analysis and a white count. The latter might be quite revealing in a patient with fever, sore throat or localizing pain. An elevated leukocyte level would favor the diagnosis of a bacterial infection and indicate a need for prompt treatment. A low count could suggest a viral illness requiring only supportive care.

Now, a modern, efficient office organization usually has an associated or nearby laboratory complex where a blood sample can be processed by automated analyzers in a matter of minutes for dozens of components. One drop of blood will yield a printout of levels of erythrocytes, hemoglobin, hematocrit, erythrocyte indices, leukocytes and platelets; another drop in another machine will provide a prompt differential of the leukocytes. And, if desired, a sample of plasma or serum can be obtained from the same venipuncture and this analyzed for a dozen or more chemical components of the blood. If an abnormality is shown, it may indicate the need for further observation or even early treatment of an unsuspected disease. However, the unusual finding may be an error or only slightly beyond the limits of normality causing some concern and the need for repeating the test once or twice. This requires another venipuncture, not always simple in a small child or infant, and another visit since the laboratory report rarely is obtained while the patient waits. Finally, the cost of a simple white count used to be only a few dollars; the charge for the complete blood count by an analyzer may be $10 or more. The chemical analyses would probably add at least $20 to the costs.

The simple, the lowly white count can be the most helpful as well as the cheapest laboratory measurement for the practitioner to do, using a drop of blood obtained by a finger-stab or small venipuncture. Sometimes the white count may show an underlying abnormality that cannot be diagnosed otherwise.

As reported in the Specialty Conference elsewhere in this issue of the journal, neutropenia in childhood is an important abnormality whose significance cannot be treated lightly. From the viewpoint of the most common causes that should be considered first, viral infection, particularly in the early stage, may produce a pronounced diminution in polymorphonuclear neutrophils by a variety of mechanisms including direct damage to the circulating cells or by suppression of their production in the bone marrow. The latter may appear later and be of longer duration. If viral infection is strongly suggested, it should not be treated with ordinary antibiotics as is too often done for any acute illness. There is the ever-present danger of the antibiotic's further damaging the bone marrow or initiating sensitization to the drug which will interfere with its later use. It must be recognized, however, that acute, fulminating bacterial infections can also cause toxic neutropenia and prompt parenteral therapy with antibiotics may then be necessary.

In addition to viral infections, enteric and parasitic organisms can suppress the leukocyte count. This has become important in this region lately with the entry of so many immigrants from Southeast Asia and the Far East. Salmonellosis, malaria, leishmaniasis and a variety of parasitic diseases, previously rare in this country, are now encountered and it is well to remember that patients with these disorders may present with neutropenia.

The symptomatic use of so many drugs these days, whether obtained through prescriptions or over the counter, makes it imperative to inquire about possible drug ingestion in every case of neutropenia. Also exposure to toxins and chemicals in the environment are hazards that are increasingly encountered. All of these may produce serious neutropenia and even progress to aplastic anemia.

Finally, neutropenia in childhood may be a manifestation of a congenital and chronic familial inheritable condition. There are several forms—specific disease entities. Some, like cyclic neutropenia, are fairly benign. Others are quite severe, leading to frequently recurring infections. Still others are associated with serious immunologic deficiencies that are life-threatening and require constant treatment. In such cases, it is most important to establish the diagnosis early in order to use appropriate treatment, consider the prognosis and offer genetic counseling.

In rare instances, neutropenia may be an early manifestation of a multisystem congenital disturbance such as Fanconi's anemia and Shwachman's pancreatic deficiency. Each of these requires specific therapeutic measures for the patient's survival.

As the Specialty Conference illustrates, a leukocyte count and differential in a child may disclose neutropenia that has important diagnostic, therapeutic and prognostic value for the health of the child. In this respect, the lowly white count is invaluable and should be utilized regularly.

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Precursors to the Advances in Plastic and Reconstructive Surgery

SIR HAROLD GILLIES, presiding at the First International Congress of Plastic Surgery in Stockholm in 1955, noted developments in the field and reviewed what the ancients and not so ancients in the field had achieved. When asked the question "What is the greatest plastic surgery advance in modern times?", he commented that "one is tempted to whisper *photography*."

It is true that many principles of surgery have been known for centuries and, furthermore, many advances in surgical techniques are a direct result of advances in the general field of medicine. For example, progress in fluid management, antimicrobial therapy and anesthesia has made procedures in plastic and reconstructive surgery possible, safe and applicable.

As noted in McDonald and Vasconez's Medical Progress article in this issue of the journal, notable advances have been made in the last two decades in the field of plastic and reconstructive surgery.

New vistas in craniofacial surgery have been opened by the combined skills of anesthesiologists, neurosurgeons and plastic surgeons. Craniofacial deformities thought to be beyond surgical correction are now regularly renovated through remarkable and painstaking procedures.

The combination of exacting surgical technique, refined nonreactive implantable plastics and improved antimicrobial weapons has brought us into the era of perfected, well-tolerated implants. Correction of contour defects in the face, breast reconstruction or augmentation, tendon spacing and implanting joints now occupy an incremental share of a plastic surgeon's time.

Renewed interest in the mapping of blood supply to composite units of tissue, including not just skin and subcutaneous tissue but muscle, bone and nerves, has opened the era of vascularized axial flaps, including the musculocutaneous flaps so indispensable in repairing life-threatening defects and in overcoming psychologically threatening deformities. Devising the pedicle used to sustain the blood and, often, nerve supply of the segment of tissue to be transferred has been refined and reduced to the point that often the pedicle consists only of the leash of blood vessels with or without nerves. Such islands of tissue on a vascular or neurovascular leash can be broadly useful throughout the body.

The advent of reliable microsurgical repair of small vessels and nerves has further liberated composite units of tissue as there is no longer the geographic limitation imposed by the length of the vascular tether. Parts of the body may be moved from one area to another at a considerable distance by cutting the identified nutrient vessels and anastomosing them to vessels in the recipient area. For example, parts may be moved from the foot to the hand or from the groin area to the head and neck in a single stage with only a transient and survivable deprivation of blood supply. Not only is it possible but now quite reliable to replant parts with small vessels such as fingers, the penis or the scalp when they have been separated in traumatic incidents.

More extensive and curative measures may be undertaken in the attack on malignant conditions with the knowledge that with today's armamentarium reconstruction or replacement of body units is reliably available.

With technology available to transfer autogenous component parts, the likely next advance to create a new era in all of surgery, including plastic and reconstructive surgery, will be a solution to the immunologic barrier to dependable, riskfree homologous transplantation. The sphere of limb, soft tissue unit, vascularized bone and joint, as well as whole organ transplantation will enter a new era with all its promise and problems.

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CASE REPORTS

Refer to: Writer SL, Stevens DL, Starkebaum G: Chlorthalidone-associated neutropenia. West J Med 136:59-61, Jan 1982

Chlorthalidone-Associated Neutropenia

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CHLORTHALIDONE, an oral long-acting sulfonamide diuretic, widely accepted for the treatment of hypertension and edematous states, has been associated with a low incidence of serious toxic reactions.[1,2] We report a case of reversible chlorthalidone-associated neutropenia, a rare complication reported four times previously.[3-6] An antibody-induced mechanism of neutrophil destruction was investigated, but not proved.

Report of a Case

A 63-year-old man with hypertension, arteriosclerotic heart disease, chronic bronchitis and insulin-dependent diabetes mellitus (adult onset) was receiving the following drugs for 15 months before this admission: hydrochlorothiazide, aminophylline, isosorbide dinitrate, nitroglycerin, propranolol, potassium chloride, insulin, beclamethasone inhaler, alginic acid and antacid (Gaviscon).

Three weeks before admission, treatment with hydrochlorothiazide was stopped and chlorthalidone therapy was begun. In addition, trivalent influenza vaccine A (H_1N_1) USSR, A_2 (H_2N_3) Victoria and Influenza B was given. His leukocyte count was normal at that time. Four days before admission, an upper extremity pruritic, erythematous rash, fever, dyspnea and a brief chill developed. On admission, he noted persistence of these symptoms, worsening fever, malaise and fatigue. There was no history of blood transfusions.

On physical examination the patient was found to be obese and in mild distress, but alert. His temperature was 37.3°C (99.14°F), taken orally, and an erythematous maculopapular rash was present over the biceps. There was slight prolongation of expiration with diminished breath sounds and an S_4 gallop. The hematocrit was 51 percent, the platelet count was 210,000 per cu mm, leukocyte count was 2,000 per cu mm with 2 percent metamyelocytes, 2 percent band forms, 8 percent segmented neutrophils (160 per cu mm), 3 eosinophils, 60 percent lymphocytes and 25 percent monocytes. The serum sodium value was 130 mEq per liter, potassium 3.5 mEq per liter and blood glucose 200 mg per dl. Values for serum creatinine, serum aspartate aminotransferase, lactic dehydrogenase, bilirubin and alkaline phosphatase were within normal limits, as were findings on an x-ray study of the chest and analysis of urine. Administration of chlorthalidone was stopped and a regimen of broad spectrum antibiotics (gentamicin and cefazolin) was started after appropriate cultures were started. A bone marrow aspirate and biopsy specimen obtained within 24 hours of admission showed 40 percent normoblasts, 46 percent granulocytic cells, 13 percent lymphocytes and 1 percent plasmacytes, with 2 percent myeloblasts, 11 percent promyelocytes, 11 percent myelocytes, 13 percent metamyelocytes, 9 percent band forms and no segmented neutrophils. The myeloid:erythroid ratio was 1.15:1, cellularity was in the low normal range, erythroid maturation was normal and megakaryocytes were present. As shown in Figure 1, nine days after chlorthalidone administration was stopped, polymorphonuclear neutrophil leukocyte (PMN) counts returned to normal. The localized rash rapidly resolved and cultures of blood, urine and sputum were all negative. Antibiotic therapy was discontinued after the granulocyte count became greater than 500 per cu mm; a normal count was documented on the ninth hospital day. Subsequently, the patient has done

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ABBREVIATIONS USED IN TEXT

PMN = polymorphonuclear neutrophil leukocyte

RAHPA = rabbit antihuman PMN antibody

well for ten months while receiving the original drug regimen, except that furosemide was used instead of chlorthalidone.

Materials and Methods

PMN Bound IgG and Serum IgG PMN-Binding Activity

The amount of IgG bound directly to purified patient PMN and normal PMN, and the amount of IgG bound to normal PMN after in vitro incubation with the patient's or normal serum were determined with the ^{125}IFab anti-F(ab)'$_2$ technique, as previously described.[7,8]

Antineutrophil Antibody Assayed by Chemiluminescence

Purified human PMN (5×10^5) was incubated with 100 μl of rabbit antihuman PMN antibody (RAHPA), normal serum or patient serum in the presence of 10^{-7} M luminol in 1.0 ml of phosphate-buffered saline at pH 7.4. Light production or chemiluminescence was monitored as counts per minute in a Beckman LS-100c liquid scintillation counter in the out-of-coincidence mode at 3-minute intervals for at least 30 minutes.

Functional Metabolic Capacity of Serum Treated PMN

After two hours incubation with the above serum preparation, 30 μl of opsonized zymosan was added to the reaction vials and chemiluminescence was observed over an additional 30 minutes.

Immunofluorescence Studies

Patient's bone marrow cells, as well as peripheral blood granulocytes, were fixed to glass slides by air drying, incubated with either normal serum or patient's serum with and without chlorthalidone at 37°C for ten minutes and washed twice with normal saline. Fluorescein-tagged caprine anti-human IgG, IgM or IgA (Becton-Dickinson, Cockeysville, Maryland) was diluted 1:8 or 1:32 in phosphate-buffered saline and flooded onto the slides, incubated for ten minutes at 37°C in a humidity chamber, washed twice with phosphate-buffered saline, mounted in buffered glycerol and examined with an American Optical fluorescence microscope.

Results

Direct PMN Bound IgG and Indirect Serum IgG PMN Binding Activity

The patient's PMN were purified when his PMN count was 96 per cu mm on day six of his hospital stay. His PMN-bound IgG was 15.3 ± 3.1 ng IgG/10^6 PMN (mean $\pm$ 1 SD) which is not significantly different from the normal value of 14.3 ± 4.6 ng IgG/10^6 PMN as previously published.[7] Also, his serum IgG PMN-binding activity was 31.8 ± 1.3 ng IgG/10^6 PMN, which was within two standard deviations above the mean for normal sera, 20.0 ± 6.7 ng IgG/10^6 PMN.[7]

Antineutrophil Antibody Assayed by Chemiluminescence

Table 1, column A, illustrates that RAHPA induced PMN chemiluminescence but that preim-

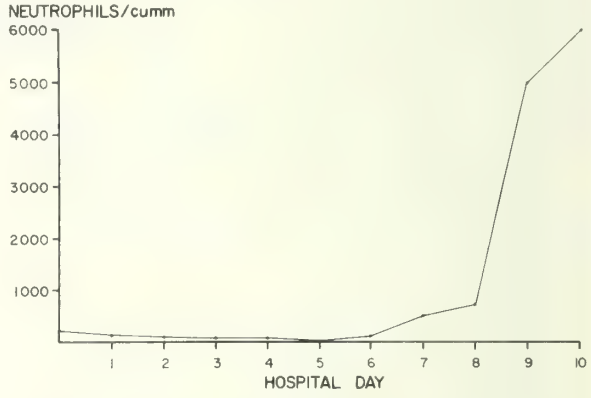

Figure 1.—Course of leukocyte response.

TABLE 1—*Studies on Antineutrophil Antibody Induced Human PMN Chemiluminescence*

	*Chemiluminescence (CPM×10⁻⁴)**	
Serum Preparation	*Peak Response to Serum Preparation (30 minutes) A*	*Peak Response of Pretreated PMN in Response to Opsonized Zymosan† B*
Normal serum	2.2±0.1	>100‡
Patient serum	2.0±0.1	>100
Patient serum§ chlorthalidone	2.5±0.1	>100
Normal serum§ chlorthalidone	3.0±0.1	>100
Rabbit antihuman-PMN serum	20.0±0.3	11.0

*The data are expressed as the mean ± SD based upon triplicate values determined in one experiment.

†After two hours preincubation of human PMN with serum, serum-opsonized zymosan was added and chemiluminescence was recorded for an additional 30 minute period.

‡Represents the maximum counting capacity of the Beckman LS-100 c counter.

§Chemiluminescence measured for 30 minutes after addition of serum only.

mune rabbit serum, normal human serum and patient serum with and without chlorthalidone did not.

Functional Metabolic Capacity of Serum Treated PMN

Table 1, column B, shows that PMN treated with RAHPA for two hours could not mount a chemiluminescence response to opsonized zymosan. In contrast, PMN treated with normal rabbit sera or patient sera with and without chlorthalidone were apparently metabolically intact since they were producing chemiluminescence intensity of greater than 1×10^6 counts per minute within 10 to 12 minutes (Table 1, column B).

Immunofluorescence Studies

Neither bone marrow cells nor peripheral blood granulocytes showed evidence of antineutrophil antibody by the indirect immunofluorescence technique. Addition of chlorthalidone to the patient's serum also failed to result in a positive indirect immunofluorescence of these cells.

Comment

That chlorthalidone was the offending drug in our patient is suggested by the development of granulocytopenia within three weeks of exposure to that drug and the prompt resolution upon stopping administration of the drug. None of the other drugs being taken by the patient, including the influenza vaccine, have been reported to cause neutropenia.[9] Furthermore, his leukocyte count has remained within normal limits after restarting therapy with these drugs. Sulfonamide antibiotics have frequently been associated with neutropenia with an incidence as high as 0.5 percent to 1 percent in some series, whereas the nonantibacterial sulfonamides (chlorothiazide, tolbutamide, chlorpropamide, acetazolomide and chlorthalidone) have rarely been reported to cause granulocytopenia in spite of their widespread use.[2,9]

In previous reports the onset of neutropenia has occurred after four to five weeks of chlorthalidone administration with a total dose of 1,000 to 3,000 mg.[3-6] Our case was similar since the total chlorthalidone dose was 2,300 mg. The mechanism of neutropenia caused by chlorothalidone was not established by these studies. Although the bone marrow findings were compatible with destruction of mature granulocytes as opposed to cytotoxicity of myeloid precursor cells, in other studies of neutropenic patients the bone marrow examination has often not been useful in determining the mechanism of neutropenia.[10,11] Furthermore, the normal levels of PMN-bound IgG and serum IgG PMN-binding activity, the lack of serum anti-PMN activity by chemiluminescence and immunofluorescence, and the failure to find PMN phagocytosis by marrow histiocytes[12] suggest that the patient's neutropenia was not due to increased peripheral destruction by a humoral immune mechanism. In addition, a haptene-dependent antineutrophil immune mechanism was not operative since no increase in anti-PMN activity was found by adding chlorthalidone. Finally, the patient's serum with or without chlorthalidone did not deleteriously affect the functional capacity of PMN to respond metabolically to opsonized zymosan.

Autoantibody to bone marrow precursor cells could not be shown by indirect immunofluorescence in the presence or absence of chlorthalidone. This finding, however, does not rule out other mechanisms of immune suppression of bone marrow granulocyte colony growth; nor does it exclude the possibility that an intermediate metabolite of chlorthalidone may have been responsible for immune peripheral destruction of PMN's or immune marrow suppression. Recent studies of a case of quinidine-induced pancytopenia described a serum inhibitor of in vitro marrow granulocytic and erythroid colony growth in spite of the fact that serum from this patient likewise had normal levels of IgG PMN-binding activity.[13]

REFERENCES

1. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics, 5th Ed. New York, Macmillan, 1975, pp 829-832

2. Wintrobe MM: Clinical Hematology, 7th Ed. Philadelphia, Lea and Febiger, 1974, pp 1290-1301

3. Plumridge RJ: Agranulocytosis due to chlorthalidone. Aust J Pharm 54:486, 1973

4. Klein M: Agranulocytosis secondary to chlorthalidone—Report of a case. JAMA 184:310, 1963

5. Turner NA, Woodliff HJ: Neutropenia associated with chlorthalidone therapy. Med J Aust 1:361, Mar 1964

6. Neaverson MA: Neutropenia due to chlorthalidone. Lancet 2:208, Jul 1964

7. Starkebaum G, Singer JW, Arend WP: Humoral and cellular immune mechanisms of neutropenia in patients with Felty's syndrome. Clin Exp Immunol 39:307-314, 1980

8. Starkebaum G, Arend WP: Neutrophil binding immunoglobulin G in systemic lupus erythematosus—Evidence for presence of both soluble immune complexes and immunoglobulin G antibodies to neutrophils. J Clin Invest 64:902-912, 1979

9. Martin FW: Hazards of Medication, 2nd Ed. Philadelphia, JB Lippincott, 1978, pp 314-316

10. Dancey JT, Brubaker LH: Neutrophil marrow profiles in patients with rheumatoid arthritis and neutropenia. Br J Haematol 43:607-617, 1979

11. Dancey JT, Brubaker LH: Neutrophil marrow function in chronic benign idiopathic neutropenia. Am J Med 68:251-254, 1980

12. Min-Fu Tsan, Mehlman DJ, Green RS, et al: Dilantin agranulocytosis and phagocytic marrow histiocytes (Letter). Ann Intern Med 84:710, Jun 1976

13. Kelton JG, Huang AT, Mold N, et al: The use of *in vitro* techniques to study drug induced pancytopenia. N Engl J Med 301:621-624, 1979

Refer to: Flick AL: Arteriohepatic dysplasia: A 16-year follow-up during treatment with cholestyramine. West J Med 136: 62-65, Jan 1982

Arteriohepatic Dysplasia: A 16-Year Follow-up During Treatment With Cholestyramine

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THIS REPORT PRESENTS 16 years of a clinical history of a patient with liver abnormalities. Although partial intrahepatic biliary atresia was the first diagnosis, this was corrected to arteriohepatic dysplasia following publication recently of an article by Riely and associates.[1] The prolonged history of the disease, liver biopsy studies over 15 years, cholestyramine therapy for 16 years and the finding of anatomic features new to this syndrome warrant this case report.

Report of a Case

The patient, a woman now 19 years old, was first seen by the author in 1965 when she was 3. Symptoms then were continual diarrhea, pruritus and elevated temperatures. Both parents are American Jews of Ashkenazi background; a single female half-sibling is normal. Pregnancy was uneventful. Birth was full term with a weight of 3 kg (6 lb, 10 oz). Neonatal jaundice was recorded, with a bilirubin of 6 mg per dl that by 3 weeks of age was 1.8 mg per dl. Pruritus was first noted at 3 weeks. By 8 weeks of age, a heart murmur and bulky stools were described and intermittent heterotropia was noted soon thereafter. Developmental landmarks were normal; the infant sat at 7 months and walked and began to use single words at 15 months.

On physical examination in 1965 the child was noted to be irritable and had excoriations over her body. Weight was 14 kg (31 lb), height 95 cm (37 in). A pulmonic systolic murmur was heard. Liver and spleen were not felt and the rest of the physical examination showed no abnormalities. Laboratory findings (Table 1) suggested cholestasis. She was admitted to hospital for study. Gallbladder series and intravenous cholangiogram gave normal findings, as did a biopsy of the small bowel. Liver biopsy showed "intrahepatic ductal atresia" (Figure 1).

Among the laboratory test results obtained at that time were a 24-hour fecal fat of 37 grams (average less than 6 grams per 24 hours), a serum calcium of 9.8 mg per dl, and a serum bile acid of 4.4 mg per dl. Following that hospital stay a serum protein-bound iodine of 6.8 μg per dl was obtained.

While in hospital, a cardiac consultant diag-

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TABLE 1.—*Selected Laboratory Test Results Over 16 Years*

	Liver Function Tests				*Treatment*		
Date	*Cholesterol mg/dl*	*Bilirubin mg/dl*	*SGOT Units/ml*	*Alkaline Phosphatase Units/ml*	*Cholestyramine*	*Phenobarbital*	*Prednisone*
1963 (born)	..	6.0	..	..			
1963 (3 mos)	..	1.5	..	..			
1965	360	2.2	120	30*			
1967-1968	..	1.6	225	60*			
1970	260	..	100	120*			
1976	263	..	159	1,350†			
1978	..	..	106	1,060†			
1979, Feb	254	0.6	94	620†		15 mg q.i.d.	
1979, May	..	..	83	547†			40 mg
1979, Jun	..	..	..	137†			
1979, Jul	296	..	81	165†			
1979, Oct	299	..	64	283†			15 mg
1979, Nov	320	..	76	160†			
1980	..	..	..	..			
1981	255	0.7	84	242†			

*King-Armstrong Units.
†International Units.

nosed pulmonic stenosis. A final diagnosis of partial intrahepatic atresia was made. Cholestyramine one teaspoon three times daily was prescribed, with replacement of fat-soluble vitamins in the form of standard cod liver oil capsules twice daily and vitamin K. This relieved the pruritus and further fever did not occur. The diarrhea lessened.

Several events of note followed over the intervening years. Severe dental caries were evident by age 5. Surgical operation for heterotropia was required by age 10, at which time an erythrotoxin was also noted. Headache and apparent papilledema led to a neurology consultation with a resultant diagnosis of pseudotumor cerebri at age 11. This condition subsided without treatment. Repeat symptoms of cystitis led to a urologic consultation at age 13, at which time intravenous pyelography was done, showing reduplicated ureters and renal pelves (Figure 2). Menses occurred normally by age 14.

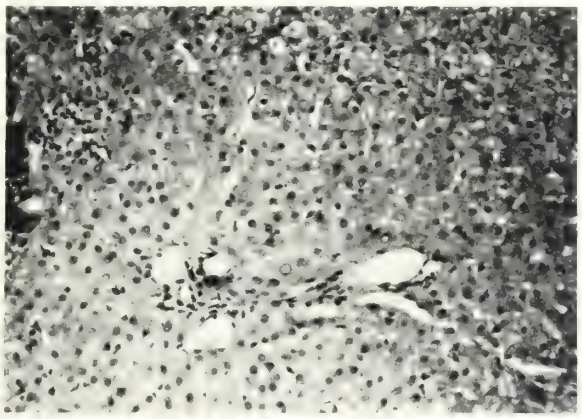

Figure 1.—Microphotograph from percutaneous liver biopsy, 1965, age 3 years, portal triad. The portal vein is easily recognized. Structures suggesting bile ducts can be seen but are not definitely identified. Focal mononuclear infiltrate is noted. (Reduced from magnification ×100.)

Figure 2.—Intravenous pyelography film showing reduplicated renal pelves and ureters.

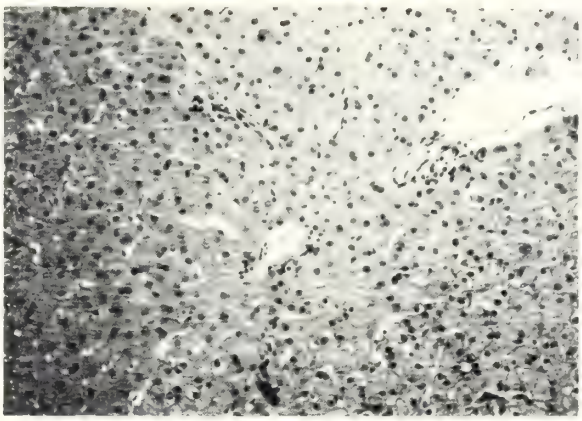

Figure 3.—Microphotograph from percutaneous liver biopsy, 1979, age 17 years, portal triad. A normal bile duct is seen (reduced from magnification ×100).

Efforts to withdraw cholestyramine led to recurrent pruritus whenever attempted. At age 16 a liver biopsy was again done and this time the biopsy specimen was normal (Figure 3). A gallbladder study likewise gave normal findings (Figure 4). A roentgenogram of the chest did not show abnormalities in heart contour (Figure 5). A three-month course of phenobarbital, 15 mg four times daily, and a five-month course of prednisone at a slowly declining dosage from an initial dose of 40 mg daily were instituted. Liver function tests remained abnormal, although the alkaline phosphatase showed substantial improvement (Table 1). Phenobarbital and prednisone were then discontinued. In late 1980 administration of cholestyramine was also discontinued, this time without recurrence of the pruritus.

The patient graduated from high school without difficulty. She engages in normal activities including a full range of physical pursuits. She appears normal, although of small stature like the rest of her family. Her facies appear normal (a photograph was declined). The murmur persists unchanged, but she has no signs of heart impairment.

Key laboratory tests are noted in Table 1. Par-

ticular attention is directed to the persistent abnormality of the serum glutamic oxaloacetic transaminase (SGOT, also known as serum aspartate aminotransferase) and serum cholesterol. An improving trend is seen for the serum alkaline phosphatase.

Discussion

This case report adds additional findings to the syndrome first described by Watson and Miller in 1973[2] and later by Alagille and co-workers in 1975.[3] Watson and Miller described the cases of 26 children from five families. Of the 26 children, 5 seemed normal, 11 had liver involvement, 14 had cardiac abnormalities, and 9 had both liver and heart abnormalities. Following jaundice at birth, liver disease tended to be mild, although pruritus sometimes persisted and the liver function tests sometimes remained abnormal. Hepatomegaly was not a regular feature and liver biopsy often gave normal findings. One case was reported in which the patient lived to age 20. Skeletal abnormalities, a characteristic facies and a bifid renal pelvis were described as associated features. Watson and Miller cited a probable similar case described by Vermassen and Buddaert in 1962. Watson and Miller concluded that they were describing a new syndrome that was familial, with predominant cardiac and hepatic features, of variable penetrance, and with occasional associated skeletal and renal features. The entity was generally rather benign.

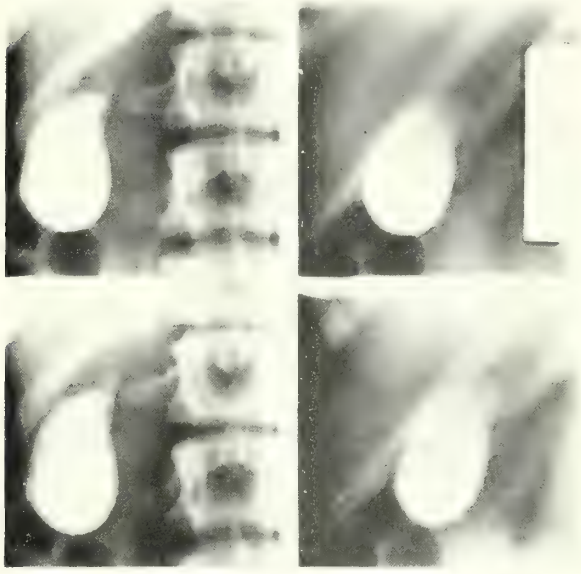

Figure 4.—Film of normal oral cholecystogram, 1978.

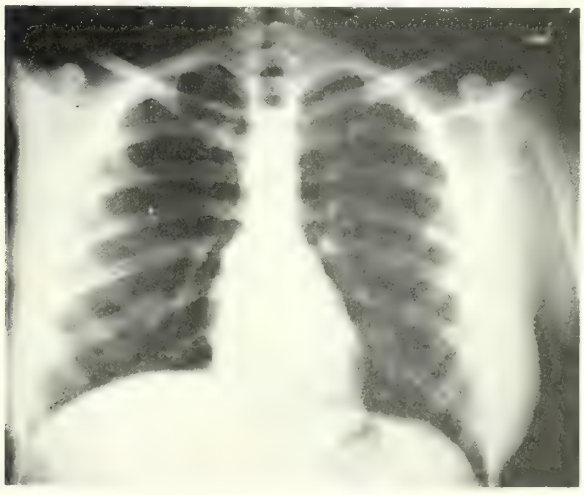

Figure 5.—Film of normal roentgenogram of the chest, 1978.

Alagille's group[3] apparently independently described the same entity in 1975. Earlier reports from this group in 1969[4] and again in 1970[5] did not focus separately on the subgroup with heart murmurs, skeletal abnormalities and the more benign clinical outcome. Other authors reporting the same syndrome include Greenwood and co-workers[6] in 1976 and Henricksen and colleagues[7] in 1977.

Arteriohepatic dysplasia is distinct from the forms of congenital cholestasis described in 1951 by Ahrens and associates[8] and grouped under the heading of atresia or dysplasia of the intrahepatic bile ducts. Ahrens' series and similar subsequent ones refer to a serious progressive disease with jaundice, xanthomas and death.

Special attention should be given to Lottsfeldt and co-workers'[9] case report; J. B. Carey, Jr., a coauthor, here extended the use of his cholestyramine from its application in primary biliary cirrhosis to intrahepatic atresia.

Summary

The case reported here adds the following information to the entity of arteriohepatic dysplasia: (1) A 13-year interval between two liver biopsies is available, with no morphologic liver abnormality found. (2) Reduplicated ureters are described for the first time in this entity. (3) Serum liver function tests gave persistently abnormal findings, including hypercholesterolemia. (4) A 15-year period of continuous use of cholestyramine, supplemented with fat-soluble vitamin replacement, appeared to have no effect on liver, bone, teeth or sexual maturation. (5) It was possible to dis-

continue therapy with cholestyramine after many years of administration.

REFERENCES

1. Riely C, Collier E, Jensen P, et al: Arteriohepatic dysplasia: A benign syndrome of intrahepatic cholestasis with multiple organ involvement. Ann Intern Med 91:520-527, Oct 1979
2. Watson DH, Miller V: Arteriohepatic dysplasia. Arch Dis Child 48:459-466, Jun 1973
3. Alagille D, Odièvre M, Gautier M, et al: Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental and sexual development and cardiac murmur. J Pediatr 86:63-71, Jan 1975
4. Alagille D, Habib EC, Thomassin N: L'atrésie des voies biliaires intrahépatiquès avec voies biliaries extrahépatiques permeables chez l'enfant. Journees Paris Pediatr pp 301-318, 1969
5. Alagille D, Thomassin N: L'atrésie des voies biliares intrahépatiques avec voies biliaires extrahépatiques permeables chez l'enfant. Rev Med Chir Mal Foie 45:93-104, 1970
6. Greenwood RJ, Rosenthal A, Crocker A, et al: Syndrome of intrahepatic biliary dysgenesis and cardiovascular malformations. Pediatrics 58:243-247, Aug 1976
7. Henriksen M, Langmark F, Sorland S, et al: Hereditary cholestasis combined with peripheral pulmonary stenosis and other anomalies. Acta Paediatr Scand 66:7-15, Jan 1977
8. Ahrens, EH Jr, Harris RC, MacMahon HE, et al: Atresia of the intrahepatic bile ducts. Pediatrics 8:628-647, Nov 1951
9. Lottsfeldt FI, Knivit W, Aust JB, et al: Cholestyramine therapy in intrahepatic biliary atresia. N Engl J Med 269:186-189, Jul 25, 1963

Refer to: Shragg TA, Albertson TE, Fisher CJ Jr: Cyanide poisoning after bitter almond ingestion. West J Med 136:65-69, Jan 1982

Cyanide Poisoning After Bitter Almond Ingestion

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ACUTE CYANIDE POISONING occurs relatively infrequently.[1] With the increasing use of amygdalin (commonly known as Laetrile) and other cyanogenic glycosides for alternative cancer therapy, accidental cyanide poisoning may become more common. Because of its rapid onset and the highly lethal nature of cyanide, many patients die before getting medical care.[1] Unfortunately, even when patients do obtain medical care the correct diagnosis is often delayed until well into their hospital course.[2,3] In reporting a case of cyanide poisoning, Graham and colleagues[2] noted the paucity of cases in which cyanide blood levels had been reported. They further questioned the efficacy and safety of the traditional therapy of intravenous sodium nitrite and sodium thiosulfate. We have recently treated a severe case of cyanide poisoning in which cyanide blood levels and the response to therapy were well documented.

ABBREVIATIONS USED IN TEXT

$A\text{-}aO_2$ = alveolar-arterial difference in oxygen
CVP = central venous pressure
FIO_2 = fraction of inspired oxygen
PCWP = pulmonary capillary wedge pressure
$\dot{Q}s/\dot{Q}t$ = right-to-left intrapulmonary shunt
SEM = standard error of the mean
$T_{1/2}$ = cyanide half-life in blood

Report of a Case

A 67-year-old woman weighing 60 kg (132 lb) was diagnosed as having carcinoma of the large bowel a year before the hospital admission described in this report. The tumor was judged to be resectable, but the patient refused either surgical therapy or consideration of chemotherapy. Eight months before admission to hospital, for a two-month period she self-administered injectable Laetrile purchased in Mexico. Subsequently, because of the expense of the injectable form, the patient switched to Laetrile tablets. The tablets were taken erratically but probably on an average of every other day over the next six months. Two weeks before the onset of her present illness, the patient was given a bag of bitter almonds by a friend, allegedly to help increase her "protein intake" and also for "medicinal purposes." Initially she ground up four to five bitter almonds and mixed them with water. Approximately 30 to 45 minutes after ingestion of the mixture, she became light-headed, and had nausea and vomiting with crampy abdominal pains. The symptoms subsided over the course of the evening and she felt well the next morning. On the night of admission she again made a slurry of water with 12 bitter almonds. She experienced a severe bout of crampy abdominal pain within 15 minutes after ingestion. The patient went into her bathroom and collapsed. Her daughter quickly called for an ambulance and en route to the hospital, a blood sample was taken and naloxone hydrochloride and 50 percent dextrose solution were administered, but failed to produce a response.

On arrival in the emergency room, the patient

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TABLE 1.—*Blood Gas Measurements Following Cyanide Ingestion and Treatment With Sodium Nitrite and Sodium Thiosulfate*

Duration From Time of Nitrite and Thiosulfate Treatment	Arterial Blood Gas				Serum Lactate	A-aO_2	PCWP	CVP	$\dot{Q}s/\dot{Q}t$
	FIO_2 %	PaO_2 mm Hg	$PaCO_2$ mm Hg	pH	mEq/L	mm Hg	mm Hg	cm H_2O	%
−18 min	21	71	13	7.34	14.3	63	..	..	..
0 min	6 liters (mask)	56	25	7.17	..	..	..	..	..
23 min	50 (intubated)	63	19	7.41	..	270	..	..	..
1 hr	100	262	32	7.35	..	411	..	..	..
5 hr 25 min	100	257	30	7.47	1.7	419	10	10	..
7 hr 25 min	100	203	25	7.56	..	479	..	..	..
7 hr 25 min (mixed venous)		39	30	7.52	..	..	..	12	40
9 hr 35 min	60	102	22	7.59	1.0	298	..	8	..
9 hr 35 min (mixed venous)		37	25	7.57	..	..	..	..	30
11 hr 25 min	60	194	25	7.53	.9	203	..	..	..
18 hrs	21 (extubated)	56	35	7.49	1.0	50	..	..	..
36 hrs	21	106	30	7.45	..	7	..	..	..

A-aO_2 = alveolar-arterial difference in oxygen; PCWP = pulmonary capillary wedge pressure; $\dot{Q}s/\dot{Q}t$ = right-to-left intrapulmonary shunt; CVP = central venous pressure; FIO_2 = fraction of inspired oxygen.

was totally unresponsive to verbal command or painful stimuli and was incontinent of stool. The odor of bitter almonds was detected by some observers. Her blood pressure was 138/90 mm of mercury, pulse was 128 per minute and respirations were 20 per minute and deep. Oxygen was administered by mask and one ampule of amyl nitrite was given per inhalation. Sodium nitrite (300 mg) and then 12.5 grams of sodium thiosulfate (cyanide treatment kit, Eli Lilly Co.) were given intravenously. The patient was intubated for airway protection and oxygenation. Using a large-bore tube, her stomach was lavaged until it returned clear fluid. An initial gastric lavage specimen was sent to the laboratory for qualitative analysis and a later report showed it to be 4+ positive for the presence of cyanide. A cathartic of 48 grams of sodium biphosphate and 18 grams of sodium phosphate per dl (Fleet's Phospho-Soda) and 30 grams of activated charcoal were administered through the gastric tube. Within 20 minutes of receiving the cyanide antidote, the patient became alert and responded appropriately to verbal commands. A Swan-Ganz catheter was inserted and she was monitored for the next 24 hours in the intensive care unit and treated with mechanical ventilation. On x-ray studies of the chest transient bilateral pulmonary infiltrates associated with hypoxic respiratory failure were seen. Her pulmonary status improved concomitant with clearing of her chest on roentgenogram and she was extubated after 18 hours.

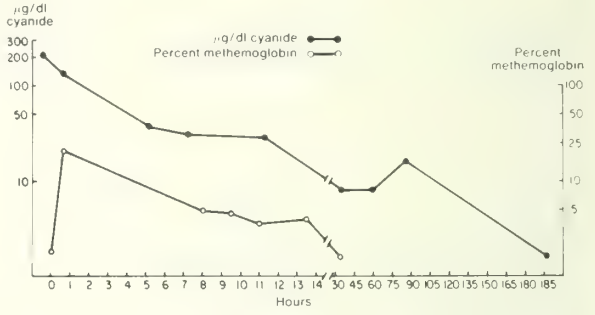

Figure 1.—Blood cyanide levels and percentage of methemoglobin are plotted against time following initiation of amyl nitrite, sodium nitrite and sodium thiosulfate treatment. The first blood specimen for cyanide level determination was drawn 20 minutes (time 0) before treatment began.

Table 1 shows arterial blood gas determinations, serum lactate levels, and the alveolar-arterial difference of oxygen (A-aO_2), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP) and right-to-left intrapulmonary shunt ($\dot{Q}s/\dot{Q}t$) obtained during her hospital stay. Cyanide and methemoglobin levels before and after treatment are displayed in Figure 1.

The remaining Laetrile tablets and bitter almonds were analyzed by Dr. Eric Conn, Department of Biochemistry, University of California at Davis. The Laetrile tablets weighed approximately 250 mg with an average amygdalin content (6 percent cyanide)[4] of 11.5 mg (±0.4 standard error of the mean [SEM]). The average weight of the bitter almonds was 1.32 grams (N = 5, ±0.04

SEM). The average cyanide content was 6.2 mg per each bitter almond (N = 5, ±0.3 SEM) or approximately 469 mg per 100 grams of bitter almonds.

Discussion

This is a case of severe cyanide intoxication after bitter-almond ingestion, complicated by lactic acidosis and pulmonary edema, that dramatically responded to aggressive supportive care and treatment with sodium nitrite and sodium thiosulfate. Graham and his colleagues[2] recently described another case of cyanide poisoning associated with lactic acidosis and pulmonary edema. They felt the level of lactic acidosis correlated with the severity of cyanide poison and could be explained by the histotoxic hypoxia associated with the cyanide poisoning. Our patient had an initial serum lactate level of 14.3 mEq per liter, which fell with therapy to a level of 1.7 mEq per liter, suggesting a substantial degree of cyanide poisoning. Further, Graham and co-workers speculated on several possible causes for the pulmonary edema but concluded that the toxic effect of potassium cyanide on the myocardium would lead to cardiac failure and high-pressure pulmonary edema. We measured PCWP in our patient and found no evidence of increased left ventricular filling pressures. Berlin[5] has suggested a central neurogenic mechanism in the previously reported case of cyanide-induced pulmonary edema. Initially our patient had an $A\text{-}aO_2$ of 63 mm of mercury, which subsequently rose to 270 mm of mercury on 50 percent fraction of inspired oxygen (FIO_2). Her inital $\dot{Q}s/\dot{Q}t$ was 40 percent with a PCWP of 10 mm of mercury. We believe our patient had pulmonary edema from altered capillary permeability. This may be the result of the toxic effect of cyanide directly on capillary endothelium or an indirect neurogenic effect leading to increased pulmonary capillary permeability.[6]

Morse and associates[7] have warned that with the increasing publicity about Laetrile, consumption of cyanogenic glycoside-containing seeds as a substitute may increase. Cyanogenic glycosides have been found in approximately 150 plant species.[8] Amygdalin, probably the best known of the cyanogenic glycosides, was first isolated from the seeds of the bitter almond.[9] Amygdalin is also present in the kernels of stone fruits such as apricots, cherries and plums.[8,9,12] The cyanogenic glycoside content within a particular type of plant may vary. Several investigators have suggested that the cyanide content of apricot pits is affected by soil conditions, watering practices and when the fruit was harvested.[8,11,12] The toxicity of amygdalin is directly attributable to the release of hydrogen cyanide. This release of cyanide occurs by mild acid hydrolysis or through the action of enzymes (β-glucosidase or emulsion) that can be found in the seeds.[9,13,14] Amygdalin yields glucose, benzaldehyde and cyanide when hydrolyzed.[14] The enzymes are not found in mammalian tissues but have been isolated from the microflora found in human intestine.[1] This probably explains why amygdalin is more than 40 times more toxic when taken orally than when taken by intravenous injection.[1]

Animal poisoning by cyanide-containing fruits and grasses has long been recognized as a problem in veterinary medicine.[15] The extent of accidental cyanogenic glycoside poisoning in humans is not known. However, there have been numerous reports of cyanide poisoning in humans from apricot pits.[11,14,16] Sayre and Kaymakcalan[14] found that the average cyanide content in the popular wild apricot seed in Turkey was 217 mg per 100 grams. This is less than half the amount of cyanide that we found in these bitter almonds. Cyanide poisoning from bitter almonds has been reported rarely.[17,18] The cyanide content found in this case of 6.2 mg per almond is similar to the 4 to 9 mg of cyanide per almond previously reported.[19]

Edwards and Thomas[3] reported the case of a 48-year-old chemist who was resuscitated after being found asystolic following the ingestion of cyanide. The cyanide level in the blood in this case of near-lethal ingestion was found to be 380 μg per dl. Recently a patient taking Laetrile experienced weakness, lightheadedness, palpitations and headaches after taking twice his usual dose.[20] An unusually high cyanide level of 600 μg per dl was found in a single blood sample taken from this patient on an outpatient basis. Unfortunately, no follow-up data were available. Normal levels of cyanide in the blood have been reported to be 10 to 20 μg per dl.[21] Toxic levels are variable but are usually considered to be over 100 μg per dl.

A minimum lethal dose of cyanide has been estimated at 50 mg[22,23] or 0.5 mg per kg of body weight.[24] The calculated lethal dose based on the weight of the patient in this report would be 30 mg. From the number of almonds she reportedly ate, it is estimated that she ingested at least 70 to 75 mg of cyanide. The estimated amount of

cyanide ingested, the high level of cyanide in the blood, the strongly positive qualitative test on the gastric aspirate, and the drastic clinical condition of the patient when she arrived in the emergency department all strongly support a case of potentially lethal ingestion. Although the patient had been taking a cyanide-containing compound sporadically over the preceding eight months, her acute symptoms developed only on the two occasions when she ingested bitter almonds. This indicates acute rather than chronic poisoning.

The mechanism of cyanide poisoning has been well described.[4] Hydrogen cyanide interrupts the electron transport at the cytochrome *a* to cytochrome a_3 step. The resultant binding of cyanide to cytochrome oxidase inhibits cellular oxygen metabolism (histotoxic hypoxia), leading to cell death.

Treatment aims at decreasing the amount of cyanide available for cellular binding. Cyanide is rapidly absorbed from the gastrointestinal tract. Our patient was initially treated with both charcoal and phosphate-biphosphate after gastric lavage. Cyanide is poorly bound by charcoal, thus prevention of absorption by immediate gastric lavage or emesis is necessary.[25] The potential importance of gastric lavage can be seen in a report of a fatal case of bitter-almond poisoning, in which the stomach contents revealed a cyanide concentration of 4,380 μg per dl with the next highest concentration in the blood (312 μg per dl).[17]

Numerous antidotes for cyanide poisoning have been suggested over the years. In an 1888 report, Pedigo[26] first suggested the potential antagonism between amyl nitrite and "prussic acid" (hydrogen cyanide). He noted that amyl nitrite not only lengthened the survival period for dogs that had been given cyanide but also provided some prophylactic effect if administered before a cyanide injection. Geiger[27] later suggested the beneficial effects of methylene blue in the treatment of cyanide poisoning. Using dogs, Chen and coworkers[28] compared the antidotal effects of methylene blue, sodium thiosulfate, amyl nitrite, sodium tetrathionate and sodium nitrite given alone and in combinations. Chen and his colleagues concluded that "the highest antidotal action is exhibited by the combination of sodium nitrite and sodium thiosulfate." Chen and Rose[10] later reported that 43 of 44 patients were successfully treated with the combination of sodium nitrite and sodium thiosulfate. Unfortunately, they did not measure blood cyanide levels in any of their work to document the severity of the poisoning or the efficacy of treatment.

Sodium nitrite initially changes hemoglobin to methemoglobin, which binds cyanide. Methemoglobin can also reverse the cyanide inhibition of cytochrome oxidase activity in vitro by complexing with cyanide to form a cyanomethemoglobin compound.[29] Thiosulfate then combines with the cyanide-methemoglobin complex and a relatively nontoxic compound is then formed in the presence of rhodanese. The use of sodium nitrite is not without potential toxicity. Berlin[30] reported a case of a 17-month-old child who died as the result of massive sodium nitrite administration. The child was given 450 mg of sodium nitrite, producing a calculated methemoglobin level in excess of 90 percent. Bodansky[31] has estimated that blood concentrations of less than 30 percent methemoglobin produce no symptoms and that lethal levels must exceed 70 percent. Our patient received the recommended adult dosage of 300 mg of sodium nitrite. The resulting peak methemoglobin level of 21 percent was well below the symptomatic range.

Hydroxycobalamin has also been proposed as an antidote for cyanide poisoning.[32-34] It is thought to combine with cyanide to form cyanocobalamin (vitamin B_{12}).[32] Several cases of successful clinical application have been reported.[35] It offers the advantage of little toxicity and may be even more effective in combination with thiosulfate therapy.[36,37] However, hydroxycobalamin is not available in this country in a concentrated form.[38] The cobalt salts, cobalt chloride and ethylenediaminetetraacetate (EDTA), have also been used to form clinically useful complexes with cyanide, but these salts are also not available in this country.[22,36-38]

The importance of general supportive measures in cyanide poisoning including the administration of oxygen has been stressed previously.[22,39] Maxwell[20] has noted recently the lack of pharmacokinetic data after human cyanide poisoning. One case of cyanide poisoning reported three cyanide blood levels over a period of 84 hours.[2] The first level was drawn 12 hours after admission. From these data, we have been able to calculate an estimated cyanide half-life in blood ($T_{½}$) of 66 hours. Our patient appears to have had an initial elimination-phase $T_{½}$ of 2 hours and a terminal elimination-phase $T_{½}$ estimated at 44 hours (see Figure 1). Our patient rapidly and dramatically responded to treatment with oxygen, gastric lavage

and sodium nitrite followed by sodium thiosulfate. The rapid $T_{1/2}$ of the initial phase corresponded to the time when blood methemoglobin levels were also maximum. The sodium nitrite and sodium thiosulfate treatment may have contributed to this early rapid fall in cyanide levels. It would appear that our terminal elimination phase $T_{1/2}$ of 44 hours is similar to the long $T_{1/2}$ calculated from the cyanide blood levels drawn after 12 hours in the previous case.[2] The exact contribution to the prolonged terminal phase elimination kinetics of any delayed absorption of cyanide after distal intestinal breakdown is unknown.

Conclusion

There does not appear to be an ideal antidote for cyanide poisoning. This case illustrates the successful early diagnosis and treatment of a severe cyanide intoxication associated with lactic acidosis and permeability pulmonary edema after the ingestion of a lethal amount of bitter almonds Aggressive supportive care and sodium nitrite followed by sodium thiosulfate was used. This case also demonstrates the need for frequent blood cyanide levels to document pharmacokinetics and any response to treatment. In addition to the need for further animal studies,[5] a multicenter study is needed to better evaluate the various cyanide antidote treatments alone and in combination.

REFERENCES

1. Smith RP: Toxic responses of the blood, chap 14, *In* Doull J, Klaassen CD, Amdur MD (Eds): Cassarett and Doull's Toxicology, 2nd Ed. New York, Macmillan Publishing, 1980

2. Graham DL, Laman D, Theodore J, et al: Acute cyanide poisoning complicated by lactic acidosis and pulmonary edema. Arch Intern Med 137:1051-1055, 1977

3. Edwards AC, Thomas ID: Letter to Editor. Lancet 1:92-93, Jan 1978

4. Klaassen CD: Nonmetallic environmental toxicants: Air pollutants, solvents and vapors, and pesticides, chap 70, *In* Gilman AG, Goodman LS, Gilman A (Eds): The Pharmacological Basis of Therapeutics, 6th Ed. New York, Macmillan Publishing, 1980, pp 1651-1652

5. Berlin C: Cyanide poisoning—A challenge. Arch Intern Med 137:993-994, 1977

6. Theodore J, Robin ED: Speculations on neurogenic pulmonary edema (NPE). Am Rev Resp Dis 113:405-411, 1976

7. Morse DL, Harrington JM, Heath CW: Laetrile, apricot pits, and cyanide poisoning. N Engl J Med 245:1264, 1976

8. Stoewsand GS, Anderson JL, Lamb RC: Cyanide content of apricot kernels. J Food Sci 40:1107, 1975

9. Lierner IE: Cyanogenetic Glycosides, National Research Council Publication No. 1354. National Academy of Science, pp 58-61, 1966

10. Chen KK, Rose CL: Nitrite and thiosulfate therapy in cyanide poisoning. JAMA 149:113-119, 1952

11. Gunder AE, Abrahamov A, Weisenberg E, et al: Cyanide poisoning in a child secondary to eating apricot pits. Harefuah 76:536-538, 1969

12. Montgomery RD: The medical significance of cyanogen in food stuffs. Am J Clin Nutr 17:103-112, 1965

13. György B, André L, Stehli L, et al: Direct potentiometric determination of cyanide in biological systems. Anal Chim Acta 46:318-321, Jul 1969

14. Sayre JW, Kaymakcalan S: Cyanide poisoning from apricot seeds among children in central Turkey. N Engl J Med 270:1113-1115, 1964

15. Couch JF: Poisoning of livestock by plants that produce hydrocyanic acid. US Department of Agricuture, Leaflet No. 88, Sep 1934

16. Yatziv A, Simcha S: Childhood cyanide poisoning secondary to eating apricot pits. Harefuah 76:535-536, 1969

17. Pack WK, Raudonat HW, Schmidt K: Lethal poisoning with hydrocyanic acid after ingestion of bitter almonds. Z Rechtsmed 70:53-54, 1972

18. Bonnischen R, Maehly AC: Poisoning by volatile compounds —III. Hydrocyanic acid. J Forensic Sci 11:516-528, 1966

19. Zakladu Z, Zwywnosci B, Uzthu P, et al: Semiquantitative method of determination of hydrogen cyanide in bitter and sweet almonds. Rocz Psh 24:703-705, 1973

20. Maxwell D: Increased cyanide values in a laetrile user. Can Med Assoc J 119:18, 1978

21. Niyogi SK: Drug levels in cases of poisoning. Forensic Sci 2:67-98, 1973

22. Naughton M: Acute cyanide poisoning. Anaesth Intensive Care 2:351-356, Nov 1974

23. Martindale W: The Extra Pharmacopoeia, 27th Ed. London, The Pharmaceutical Press, 1977, p 745

24. Dreisbach RH: Handbook of Poisoning, 8th Ed. Los Altos, CA, Lange Publishing, 1976, p 222

25. Arena JM: Poisoning, 4th Ed. Springfield, IL, Charles C Thomas, 1979, pp 34-35

26. Pedigo L: Antagonism between amyl nitrite and prussic acid. Med Soc Virginia 19:124-131, 1888

27. Geiger JC: Cyanide poisoning in San Francisco. JAMA 99:1944-1945, 1932

28. Chen KK, Rose CL, Glowes GA: Comparative values of several antidotes in cyanide poisoning. Am J Med Sci 188:767-781, 1934

29. Albaum HG, Tepperman J, Bodansky O: Competition of methemoglobin and cytochrome oxidase for cyanide in vitro. J Biol Chem 163:641-647, 1946

30. Berlin CM: The treatment of cyanide poisoning in children. Pediatrics 46:793-796, 1970

31. Bodansky O: Methemoglobinemia and methemoglobin-producing compounds. Pharmacol Rev 3:144-196, 1951

32. Conn JB, Norman SL, Wartman JG: The equilibrium between vitamin B12 (cyano-cobalamin) and cyanide ion. Science 113:658-659, 1951

33. Mushett CW, Kelley KL, Boxer GE, et al: Antidotal efficacy of vitamin B12 (hydroxocobalamin) in experimental cyanide poisoning. Proc Soc Exp Biol 81:234-237, 1952

34. Posner MA, Tobey RE, McElroy H: Hydroxocobalamin therapy of cyanide intoxication in guinea pigs. Anesthesiology 44:157-160, 1976

35. Yacoub M, Faure J, Morena H, et al: Acute cyanide poisoning, current data on the metabolism and treatment with hydroxocobalamine. Eur J Toxicol 71:22-29, Jan 1974

36. Evans CL: Cobalt compounds as antidotes for hydrocyanic acid. Br J Pharmacol 23:455-475, 1964

37. Isom G, Way JL: Cyanide intoxication: Protection with cobaltous chloride. Toxicol Appl Pharmacol 24:449-456, Mar 1973

38. Lovejoy FH Jr: Cyanide (Part II). Clin Toxicol Rev 2:Aug 1980

39. Burrows GE, Liu DH, Way JL: Effect of oxygen on cyanide intoxication V—Physiologic effects. J Pharmacol Exp Ther 184: 739-748, 1973

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Smoke Inhalation Injuries

TO THE EDITOR: The article by Dr. Diana Lewis Coleman on smoke inhalation in the October 1981 issue[1] is a thorough summary of the pathophysiology of inhalational injury. Several points regarding the management of such patients deserve comment.

First, Dr. Coleman downplays the fact that the majority of inhalational injuries occur in association with significant burns to the upper torso and face. In the process of resuscitation of persons with such injuries, it is common to find the development of massive facial edema over the first 24 hours in hospital. The delayed management of airway obstruction in such patients is a tenuous affair.[2,3] In the past, this situation often resulted in a tracheostomy, with the attendant marked increase in morbidity and mortality due to pulmonary sepsis introduced from this wound.[4] Given the often insidious onset of upper airway obstruction, I differ with Dr. Coleman and advocate an early elective nasotracheal intubation in the clinical setting of an inhalational and facial burn.

Second, Dr. John Head, formerly of the Massachusetts General Hospital, demonstrated the efficacy of bronchoscopy,[5] also not recommended by Dr. Coleman. It is true that the findings in an inhalational injury by bronchoscopy are inconsistent, but they are often helpful enough to a clinician to warrant this study. Dr. Head found that the combination of typical endoscopic findings (edema, soot, hemorrhage) with evidence for a capillary leakage of indocyanine green was significant for a major pulmonary injury. At the Massachusetts General Hospital we found that a bronchoscopy at the time of admission was useful in predicting the course of a respiratory injury before other tests (x-ray study of the chest, arterial blood gases, pulmonary mechanics) gave abnormal results.

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REFERENCES

1. Coleman DL: Smoke inhalation—Medical Staff Conference, University of California, San Francisco. West J Med 135:300-309, Oct 1981
2. Munster AM: The early management of thermal burns. Surgery 87:29-40, 1980
3. Trunkey DD, Blaisdell FW (Eds): Inhalation injury in burn patients (Trauma Rounds). West J Med 124:244-248, 1976
4. Eckhauser FE, Billot J, Burke JF, et al: Tracheostomy complicating massive burn injury: A plea for conservatism. Am J Surg 127:418-423, 1974
5. Head JM: Inhalation injury in burns. Am J Surg 139:508-512, 1980

The Dilemma of Nursing

TO THE EDITOR: "Private duty bartender. Jane Smith, RN, last seen as nursing care coordinator on Ward N is now a bartender. Need help with a house party? Call anytime."

The above flier was recently received, decorated interestingly with a martini glass converted into a caduceus, very artistically I might add. This nurse was making in the neighborhood of $25,000 per year, but somehow she was achieving so little personal satisfaction on her job that she decided to leave the field entirely. Perhaps nothing illustrates the dilemma of the modern nurse better than that advertising notice from a highly skilled young woman who recently resigned as head nurse at a San Francisco hospital.

In spite of a new contract just having been signed with the affiliated hospitals by the California Nurses' Association, which calls for a salary increase of over 20 percent in 18 months, the problem of nurses leaving the field is a critical one. Only 6 of 200 applicants are accepted in nursing schools and 5 of these graduate. One year after graduation, only one is working as a hospital staff nurse. Professional nursing publications and associations are appropriately alarmed. But, perusing their literature, a physician is appalled by the lack of insight: More times than not, the editorialists blame physicians for the lack of morale among nurses, completely missing the point.

Nursing is not a profession. After that bombshell, I'll explain my view further. It is plain that with the exception of nurses in special units, operating room, dialysis, emergency room and the like, hospital nurses fulfill only two functions, neither of which can be called professional. They are given administrative responsibilities for which

they are poorly trained and feel inadequate or they are given other responsibilities that they feel are demeaning. The one encompasses scheduling, making assignments, responding to doctors' orders and the like; the other includes bed making, answering call bells and emptying bedpans. Somehow in high school and in college, prospective nurses are misled and are given the idea that they will be responsible for patient care, while in practice nurses must carefully follow prescribed administrative guidelines, nursing association guidelines and physicians' orders that they may or may not agree with. The rest of the time they act as housemaids. Individual initiative has no place in this scheme.

All this adds up to the fact that nursing is no more a profession where individual responsibility is placed at a premium with commensurate reward than is bus driving or any other service that has significant personal responsibility. Nursing schools, which are now exclusively the province of universities, take great pride in separating nursing education and nursing responsibility from the field of medicine and its specialities. They attempt to justify all of this by calling nursing "a profession." When the first university nursing school was established at Johns Hopkins in the 1890's the direction was established by a nurse, separating it completely from any input from the medical staff, creating a pattern that has resulted in the virtual elimination of all nonuniversity training programs in this country. A professor of nursing with a PhD in nursing recently announced with pride when asked whether physicians take part in her educational program at a large midwestern university: "We have nothing to learn from doctors!"

A glance at the modern nursing school curriculum at any university will make it easy to understand why nursing care in hospitals is generally regarded so poorly. Recent graduates are so ill-prepared to take care of the nursing needs of a patient that they must spend two to three months in a preceptorship program in a hospital before any responsibility can be given whatsoever. Erudite term papers on the philosophy of illness and the biology of cancer prepares a nurse in no way for what she is going to face once placed on the ward. The perennial complaints of any patient in a hospital quickly confirms this. The poor preparation to deal with the patient and his everyday needs is reflected in the usual delay of nurses to answer call bells and the frequently apparent callousness in responding to patients' "unreasonable demands." Adding insult to injury, many nurses are now being requested to manage highly sophisticated computers for orders and information retrieval for which they have no particular interest or training. This is a perfect formula for the alienation of the present hospital staff nurses from their job.

Again, the unreasonable expectations and the inappropriate training of present-day hospital staff nurses is responsible for the nursing crisis, as I see it. Increasing salaries and fringe benefits will have no effect. Nursing training must shift gears. In the meantime, we shall see everyday nursing responsibilities taken over more and more by licensed vocational nurses and others who are not burdened with irrelevant education. Administrative responsibilities will be taken over by those who are particularly trained. The path has been blazed in the military where there has been a perennial shortage of registered nurses.

The nursing "profession" should be reminded of Walt Kelley's character Pogo when he said, "We have met the enemy and he is us."

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Nutrition Cultism

TO THE EDITOR: It was a pleasure to read Dr. Victor Herbert's incisive attack on nutrition quackery.[1] He correctly identifies the hazards of a 10 percent fat diet which excludes basic food groups such as milk, meat and the "energy group" (fats, alcohol and sugar). The American Medical Joggers Association reviews deaths of marathon runners, and has collected more than two dozen reports of rhythm problems associated with low-fat diets.

Our prospective study of 167 marathoning cardiac patients now represents 1,000 patient-years with deaths numbering seven (0.7 percent per year). Three of the "most improved" patients died "rhythm" ("electrical") deaths when they trained on low-fat diets. After a period of falling body weight and serum cholesterol, they experienced irregular pulse and nonspecific weakness. Although they complained of "running poorly," they usually died at or near their highest level of fitness; hence the term "elite runner's arrhythmia."[2]

As the hobbies of running and dieting become more popular, we expect to see an increase in the numbers of these "nutritional arrhythmias." The

present rate of case accumulation is about six per year. We speculate that a low-fat diet is deficient in the essential fatty acid linoleic acid, which is important in the prostaglandin pathway where it exerts antiarrhythmic effects.[3]

It is to be hoped that Dr. Herbert's attack will dampen the public's enthusiasm for fad diets.

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REFERENCES

1. Herbert V: Nutrition cultism (Informed Opinion). West J Med 135:252-256, Sep 1981
2. Bassler TJ: Body build and mortality. JAMA 244:1437, 1980
3. Bassler TJ: Weight reduction and sudden death. Am J Clin Nutr 34:1639-1640, 1981

The Value of Neurological Consultation

TO THE EDITOR: Bodily and coauthors, in their article in the September 1981 issue,[1] recommend ultrasonic arteriography "in those patients with atypical symptoms that may represent ischemic neurological events." Further, they advise that "should a significant stenotic lesion be identified, endarterectomy could then be offered. . . ." Since "significant (carotid) stenosis" is often asymptomatic, this finding, whether by invasive or noninvasive testing, does little to clarify the nature of "atypical" symptoms. Where prior neurological consultation is appropriately obtained, candidates for vascular studies with such "atypical" symptoms, should be few indeed. Those whose symptoms remain "atypical," or of uncertain significance, should be evaluated and reevaluated by appropriate consultants for as long as it takes to clarify whether or not they have organic disease and, if so, whether or not their disease is vascular. Only when a vascular basis for a patient's symptoms seems likely on clinical grounds is it appropriate to apply vascular testing.

As a neurologist, I am troubled by the increasing espousal by vascular surgeons of the nebulous concepts of "atypical" and "nonhemispheric" stroke and transient ischemic attack.[2] The difference of opinion between neurologists and vascular surgeons in regard to carotid endarterectomy is not so much a matter of conservatism versus liberalism in the application of surgical procedures as it is a frank disagreement over diagnostic concepts.

A diagnostic scheme not including prior neurological consultation neither serves the best interests of patient care nor advances knowledge of cerebrovascular disease.

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REFERENCES

1. Bodily KC, Modene VT, Chikos PM, et al: Ultrasonic arteriography: Implications in patient management. West J Med 135: 183-190, Sep 1981
2. Baker WH: The role of carotid endarterectomy. Vasc Diagn Ther 2:19-24, Feb/Mar 1981

Palindromic Asymmetric Polymyalgia Rheumatica

MOST AUTHORITIES consider that a diagnosis of polymyalgia rheumatica can be made clinically on the basis of aching, stiffness and tenderness of proximal musculature, as well as prominent morning stiffness of at least one month duration in middle-aged to elderly patients with elevated sedimentation rates.[1] I wish to describe a case that fulfills the above criteria, yet the patient presented with well-defined asymmetric clinical attacks.

An 82-year-old white woman was evaluated for hypersomnia, a weight loss of 4½ pounds (from a base of 87 pounds), and episodic shoulder and hip girdle muscular stiffness and soreness. The musculoskeletal symptoms had been present for six months before the consultation. During the month preceeding her presentation, the symptoms had become well-defined into attacks that lasted for three to four days, resulted in almost total immobility and were separated by approximately one-week intervals during which there was a relative return of function. In addition, the attacks occurred predominantly on the right side. The patient had noted no cranial symptoms suggestive of temporal arteritis. She was otherwise well and had not seen a physician in many years.

On physical examination there was no synovitis or muscle tenderness or weakness but decreased mobility of the shoulder and hip joint was noted. The remainder of the findings were noncontributory. Laboratory studies showed a Westergren sedimentation rate of 80 mm per hour (repeat of 86 mm per hour), normal complete blood count and chemistry panel, normal free thyroxine index and absent rheumatoid factor. The patient was begun on a regimen of prednisone (30 mg a day by mouth) and within two to three days there was a dramatic clinical response with greatly increased mobility and disappearance of muscular soreness. Sedimentation rate decreased promptly and has stabilized at approximately 35 mm per hour. During the past five months, the prednisone

has been tapered to 15 mg every other day, and she has continued to do very well clinically.

Recent publications have emphasized unusual presentations of polymyalgia rheumatica and temporal arteritis.[2,3] The above case shows that even the more traditional presentations can vary from patient to patient. A literature search has failed to find previous reports of palindromic or asymmetric polymyalgia rheumatica. Further definition of these variations and their frequency may be useful in allowing patients to receive therapy for this eminently treatable disorder.

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REFERENCES

1. Bird HA, Esselinckx W, Dixon ASTJ, et al: An evaluation of criteria for polymyalgia rheumatica. Ann Rheum Dis 38:434-439, Oct 1979
2. Klein RG, Hunder GG, Stanson AW, et al: Large artery involvement in giant cell (temporal) arteritis. Ann Intern Med 83: 806-812, Dec 1975
3. Cheny JE, Pearce JMS: Unusual variants in the presentation of temporal arteritis. Postgrad Med J 56:88-91, Feb 1980

Women in House Staff Training Programs

To the Editor: Recent reports[1,2] have described the increased impact of women physicians in medicine. We would like to add another dimension to this reported experience by noting the prevalence of women in the house staff training programs at the Kaiser-Permanente Medical Center in Santa Clara, California. This hospital is part of Stanford University's affiliated programs for graduate medical education in pediatrics, general surgery and the surgical specialties, and has independent programs in obstetrics and gynecology and internal medicine (affiliated for medical student teaching).

The medical house staff consists of 22 full-time residents, 4 first-year residents in psychiatry from Stanford University, who spend six months on medicine, and a chief medical resident. Of the 22 full-time medical residents, 18 (82 percent) are women. Of this year's entering residents, 100 percent (all eight) are women. Women make up 44 percent (four of nine) of the obstetrics and gynecology house staff.

We can only speculate on the reasons for this prevalence. Chance probably is one factor. Another might be the noncompetitive and strong clinical orientation of the programs, or the flexible structure of the medicine program, which also allows considerable time for personal needs (night call every fifth night and a night float system, for example).

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REFERENCES

1. Relman AS: Here come the women. N Engl J Med 302:1252-1253, 1980
2. Braslow JB, Heins M: Women in medical education: A decade of change. N Engl J Med 304:1129-1135, 1981

Iron Deficiency Therapy and General Nutrition

To the Editor: We commend the interesting and thorough paper "Iron Deficiency: Diagnosis and Treatment"[1] by Dr. Peter R. Dallman in the June 1981 issue. We would add only two precautionary notes from a nutritional point of view. First, iron therapy can affect the absorption of other essential nutrients[2] and for this reason should be lowered when the anemia is eradicated and discontinued as soon as the patient's iron stores are deemed adequate. Second, it must be remembered that the dietary recommendations in Dr. Dallman's paper pertain to patients with clinical problems and are not appropriate for the healthy, normal population. (For example, to limit dairy foods with an eye towards enhancing iron absorption would, in a person not at iron risk, limit access to calcium, riboflavin, and vitamins A and D, nutrients not abundantly available in our food supply otherwise.)

Dietary recommendations limiting the intake of any of the basic four food groups during iron therapy should be discontinued as soon as the iron deficiency has been eradicated, and the complete exclusion of any major food group during iron therapy should definitely be discouraged.

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REFERENCES

1. Dallman PR: Iron deficiency: Diagnosis and treatment (Nutrition in Medicine). West J Med 134:496-505, Jun 1981
2. Solomons NW, Jacob RA: Studies on the bioavailability of zinc in humans: Effects of heme and nonheme iron on the absorption of zinc. Am J Clin Nutr 34:475-482, Apr 1981

Competition and Professionalism

To the Editor: There is an increasing feeling of uneasiness in the current attempt to indoctrinate the practitioner with economic guideposts to his professional conduct. Such erosion of professionalism is implicit in a cold dollar-centered judgment of medical care—a judgment that does not reflect

the public's preferred goal of a worthwhile life with good health. Subtle indoctrination, which encourages a shift away from the conduct of a professional who is meant to tend the ill to a man whom the economists counsel to tend the cash register for society, should be viewed with concern.

Practitioners should, of course, be accountable where waste and inefficiency surface. The move from the hospital back to the office for appropriate diagnostic and surgical procedures is part of such accountability (despite the increased malpractice liability). Furthermore, the move away from the costly emergency rooms exposes the economic and medical fallacies of the mandatory specifications from the Hill-Burton bureaucracy for such service.

The recent emphasis on the cost-benefit relationship derives from the bureaucratic concept of medical care as an industry or business. Few will deny that the legislative component of the government has been and so far continues to be a significant part of the problem of the high cost of patient care. The thought occurs that a rudimentary political medicine is being worked out from heretofore ruinous political economics, oblivious of the conflict between price and medical efficacy.

The economists' inroads into patient care are justified on the grounds that there is a similarity in market procedures to medical care and commercialism. There is, of course, a limited role for the market in medical care—for example, supplies, food, laundry, armamentaria, maintenance and nonprofessional labor. No activity, commercial or professional, can subsist without some such requirements. The elemental fact, however, remains that the material, the product and the result are not comparable.

Competition, currently being promoted as the key to cost containment of medical care (as noted in the editorial "Competition in the Health Care Enterprise"[1] in August), is of two kinds: (1) *professional,* involving skill and competence, and (2) *price,* widely popularized by Professor A. C. Enthoven, whose discipline (economics) by its very nature is relevant to the commodities market but not to patient care. Our deepest concern that it is unprofessional to compete in price, long held as the foundation of all professionalism, was singled out for legal disapproval by judges unsure of its meaning and justification. (Witness the admission in a footnote to a 1975 Supreme Court decision that "professional practice was different from other [sic] business activity."[2])

Price competition is germane to commercial ventures, not professional conduct. There is a proper place for pluralistic medical care approaches to satisfy various tastes and needs. However, when the burden of participating in such ventures (with pressures exerted for cost containment) is placed upon the medical profession, there is some ground for the conclusion that it constitutes an inroad of commercialism into professionalism with what I believe to be a further deprofessionalization of the profession.

Underneath all the jargon of competition, the old truism "you get what you pay for" seems forgotten. Implied in it lies conservation—reducing the consumption of medical care to contain its cost. But what you end up with is cost-shifting; from the government, insurer and employer to the patient. The theory presupposes that if you are to pay for something from your own pocket you will shop or forego the service. That is true for commercialism, but when it comes to life and health, the human odds in most cases are against such a supposition. Note the testimony of "shoppers" from prepaid group plans. Cost reduction can be made to look good on paper, but when all the costs are added up, you will still come up with virtually the same figures for cost of medical care.

There is a direct correlation between cost and scientific and technological achievements; hence, the expectation of a solution to the high cost through competition remains to be seen. Such expectation is further in doubt through the paradoxical suggestion of controls on quality and accessibility—a costly governmental regulation that runs counter to the mood of the country in last year's election.

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REFERENCES

1. Competition in the health care enterprise (Editorial). West J Med 135:135-136, Aug 1981
2. Costillo LB: Competition policy and the medical profession (Sounding Board). N Engl J Med 304:1099-1102, Apr 30, 1981

Chinese Medicine

To the Editor: Eloquent truths are so often unconsciously spoken. This was brought home to a group of us on a recent trip to China during which we were given the opportunity to observe how Chinese medicine is practiced in their hospitals. As we passed from room to room we saw patients undergoing various forms of treatment. Some were subjected to cupping, others had warm paraffin packs on their abdomens for the treatment of

ulcers. There were rooms devoted to ultraviolet and infrared therapy. And, of course, we saw patients with needles in their ankles, wrists and earlobes, perhaps with a ginger root smouldering on the thenar eminence of the right hand.

Everywhere there was total compliance, especially in the patients undergoing acupuncture. Not a muscle moved, not an eyelid blinked, and there was never so much as a furtive glance at this troop of foreign doctors. The attending physician assured us that their treatments were highly successful. We recalled the consensus report of the President's Committee on Acupuncture. The conclusion was "Acupuncture works, in China, on the Chinese."

We progressed down the hall to the pharmacy where we were shown various materials used in the preparation of their "natural remedies." Not only do they use flowers, bark, roots and herbs, but also dried frogs, sea horses, snake skin and shark fin. These are pulverized into potions to be administered for specifically indicated diseases and disorders.

As always, at the end of such hospital tours, there was a friendly question-and-answer interchange over the traditional tea cups. It was here that two truths unfolded.

One physician, after observing patients throughout the hospital puffing away at those fat Chinese cigarettes, asked why this was permitted. The answer through the interpreter was, "The Government *persuades* but does not *prohibit*. Also, the Government owns the tobacco factories."

Truth Number One.

Another question: "We have seen various applications of Chinese medicine this morning. Do you ever use Western medicine?" The answer: "In the occasional acute case where more rapid cure is needed, yes, we will use Western medicine."

Eloquent truth Number Two. Anyhow, in America, on Americans, Western medicine works.

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Corrections: October Article by Bruce, Hossack, Belanger, et al

TO THE EDITOR: In our article "A Computer Terminal Program to Evaluate Cardiovascular Functional Limits and Estimate Coronary Event Risks"[1] in the October issue, a manuscript error resulted in incorrect regression equations on page 343.

The corrected equations should be as follows:

$\dot{V}o_2$ max = 0.056 (duration in seconds) + 3.88 for men;

$\dot{V}o_2$ max = 0.056 (duration in seconds) + 1.06 for women.

In other words the decimal point was misplaced for 0.056 and the figure was printed as 0.56. The intercept coefficient 3.99 should have been 3.88 and the sex identity for the two equations was omitted.

A second error, this one apparently a mistake by the journal's printer, was the omission of two words and a heading in Figure 2 on page 344. Under item 14, "Evidence for Heart Disease," it lists "1. Inapparent" and "2. Possible." Two other classifications—"3. Probable" and "4. Definite"—should have been included. The following section should have been headed "15. Cardiovascular Diagnosis."

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REFERENCE

1. Bruce RA, Hossack KF, Belanger L, et al: A computer terminal program to evaluate cardiovascular functional limits and estimate coronary event risks (Health Care Delivery). West J Med 135:342-350, Oct 1981

Further Correction: Formula to Calculate Serum Osmolality

TO THE EDITOR: This is just a quick note in between patients to inform you that your magazine "blew it again." I am referring to the correction for the formula to calculate serum osmolality.[1,2] In order to be correct, the number under BUN should have been 2.8 and not 28, thus the formula should read as follows:

$$2 \times Na + \frac{BS}{18} + \frac{BUN}{2.8} = \text{osmolality}.$$

Actually many clinicians use 3 instead of 2.8 because it is easier to calculate without the fraction and the result is close enough to be of practical value.

Don't despair. The journal is usually on the mark.

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EDITORS' NOTE: The normal range for serum osmolality, calculated as above, is 285 ± 4.2 mOsm per kg H_2O.

REFERENCES

1. Becker CE: Acute methanol poisoning—'The blind drunk'—Medical Staff Conference, University of California, San Francisco. West J Med 135:122-128, Aug 1981

2. Correction: Formula to calculate serum osmolality (Correspondence). West J Med 135:341, Oct 1981

Refer to: Kurtz KJ: Training the internist for primary care: A view from Nevada (Medical Education). West J Med 136:76-82, Jan 1982

Training the Internist for Primary Care: A View From Nevada

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The recent establishment of primary care residencies at the University of Nevada School of Medicine has raised important questions about local priorities in the training of physicians to provide primary care for adults. Because the amount of money available for health care training is decreasing, these questions also have national importance. Primary care internal medicine, not synonymous with general internal medicine, offers distinct advantages to patients over family practice adult care and primary care offered by internist subspecialists. The University of Nevada has a singular opportunity to organize a strong primary care internal medicine residency, but national problems of internal medicine emphasis exist. Nationwide changes in internal medicine residency programs (ongoing) and American Board of Internal Medicine nationalization of the fledgling primary care internal medicine fellowship movement are suggested. Specifically proposed is an extra year for primary care training with a single examination after four years, producing general internists with a primary care "minor." Alternately, and ideally, there would be a full two-year primary care fellowship with a separate internal medicine primary care subspecialty board examination. Either of the above options would provide necessary training and academic credibility for primary care internists, and would redirect internal medicine certification and training.

> *I would like to emphasize the fact that the student of internal medicine cannot be a specialist.*
>
> SIR WILLIAM OSLER
> *Aequanimitas*, 1897

PRIMARY CARE is the current *buzzword* in American medicine and has been the subject of frequent symposia and publications.[1-5] The current national preoccupation with primary care and the impact of future social and financial pressures on this movement have been extensively covered elsewhere.[6,7] Likewise, much has been written recently about internal medicine's dilemma.[8] Beset by maldistribution of subspecialists versus general internists[9-11] and by increasing political and monetary pressure from primary care-oriented movements such as family practice, the American Board of Internal Medicine (ABIM) is at a crossroads. Whereas 70 percent or more of internists

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ABBREVIATIONS USED IN TEXT

ABIM = American Board of Internal Medicine
SREPCIM = Society for Research and Education in Primary Care Internal Medicine

being trained should be general internists,[12] current residency programs are directing 70 percent into subspecialty fellowships,[8] producing maldistribution within the profession. At the same time, internal medicine faces an intramural challenge from a splinter faction that feels that general internists, as currently trained, are ill equipped to render primary care. So-called primary care internal medicine tracks have proliferated,[13] and a Society for Research and Education in Primary Care Internal Medicine (SREPCIM) has evolved.

When the University of Nevada School of Medicine converted to a four-year curriculum and established residency programs in the late 1970's, national priorities in primary care were just starting to change rapidly. This school is and will remain relatively small (45 students per class) and is mandated by the state legislature and other funding sources to train primary care physicians in a community-based clinical setting. Nevada has an extensive rural population that is medically underserved, and politicians see the medical school as providing the answer to this problem. Accordingly, the school expanded to four years in 1977, and residency programs in the primary care specialties of family medicine, internal medicine and pediatrics began a year later. As a young internist with an initial dual appointment in the Departments of Family and Community Medicine and of Internal Medicine, the author found it necessary to address specific, as well as general, philosophic questions about training primary care physicians. What follows is one perspective on primary care internal medicine and how physicians should be trained for adult primary care in general.

Primary Care Questions

Availability of Providers

The essence of primary care—a generalist approach to a patient, including first contact, accessibility, continuing care, comprehensive management and "commitment to people above commitment to technology"—has been discussed at length in numerous publications.[14-17] The stunning variety of definitions generally is derived from a spectrum of specialty societies claiming preeminence in the delivery of such care.[18-20] Recently, however, emphasis has shifted from the specialty of the provider to a definition of services.[21] Whatever the definition, it was once assumed that such primary care physicians were in short supply. This assumption is being questioned today. If one uses a criterion of every American having a physician who assumes continuing responsibility for most of his or her medical needs, Aiken[22] has suggested that the country will have adequate primary care physician manpower by the late 1980's. The Graduate Medical Education National Advisory Committee has compiled data indicating that some primary care areas will have adequate numbers by that time. Nevertheless, the question of appropriate quality and quantity of primary care training is valid, especially with a local mandate for new training programs in Nevada and decreased health care dollars nationally.

Family Practice and Limitations

Figure 1 shows the areas of overlap in knowledge and service spheres of those physicians

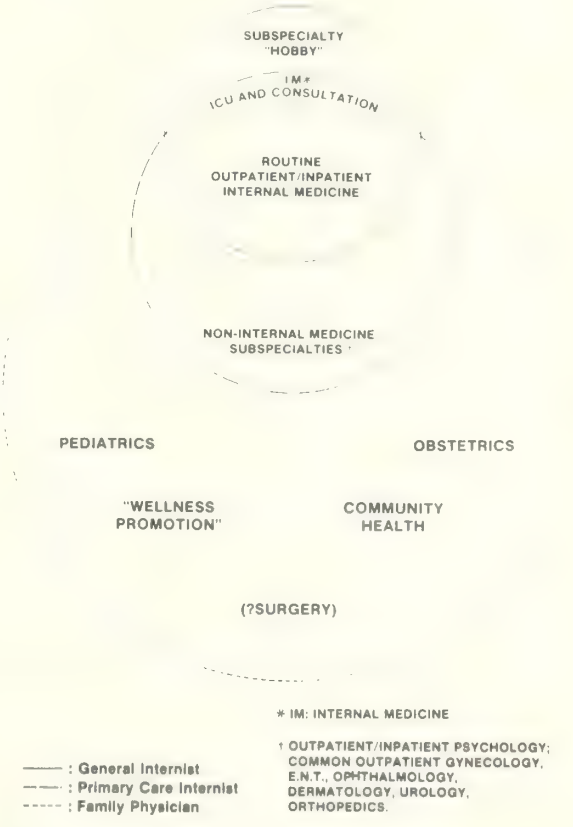

Figure 1.—Knowledge and service spheres of physicians providing primary care to adults. The overlapping circles schematically indicate *breadth*, presumably related inversely to *depth*.

theoretically best trained to deliver adult primary care. Evaluation of family practice and internal medicine qualifications and limitations is crucial to the future of primary care physician training.

Since 1966 the family practice movement has been an advocate of primary care emphasis.[9] Although terminology and definitions vary, basically family medicine studies disease and also evaluates patients, their families and their communities.[9] In an effort to further determine its future role in the American health care system, leaders of the movement recently have promoted the concept of family practice as an outpatient subspecialty.[23]

Should internal medicine abandon non-internal medicine adult outpatient primary care training to the family practice movement? Given its well-entrenched financial and political base, family practice is well situated to resist inevitable budget cuts in primary care training programs.

There are valid reasons why internal medicine should not abrogate this responsibility.

From the breadth of the family practice service sphere portrayed on Figure 1, one can see that family practice physicians are caught in the intense squeeze of modern biomedicine. One physician is responsible for, and must keep abreast of, concepts and knowledge encompassing adult internal medicine and also pediatrics, obstetrics and office surgical procedures, as well as the remaining outpatient subspecialty spectrum, all consolidated within three years of residency instruction. The result is often a very broad, but necessarily superficial, knowledge of many aspects of medicine. This may result in the paradox of increased fragmentation of individual patient care and the ultimate realization by patients that they are ill served if they become very sick.[24,25] As the level of knowledge required decreases, there is the possibility of training nurse practitioners to provide a similar service in each sector of the family practice sphere. Training such paraprofessionals is less expensive than training physicians and it is gaining momentum, especially in routine pediatrics and obstetrics. This concept is quite valid and cost efficient in the *new wave* areas of community medicine and "wellness maintenance," where complete medical doctor training is probably unnecessary.[26]

The superficiality of family practitioners' knowledge is more of a drawback in teaching resident physicians. Family practice often lacks academic credibility in large teaching centers,[27] and has self-admitted problems in providing adequate indepth resident teaching.[28] Dr. L. Robert Martin, President of the Society of the Teachers of Family Medicine, has stated that family practice residents are concerned about the quality of teaching by family physicians. He has also noted that residents often request physicians from other primary care specialties to teach in family practice centers.[28] Nor is family practice equipped to provide ever-increasing numbers of physicians. Growth in this field has probably reached a plateau, as more faculty must be trained and current programs evaluated.[8]

Primary Care Internal Medicine

Primary care internal medicine surfaced as a field of medicine a decade ago, largely because of grant availability, but also because of the above-stated feeling that family practice may not provide adequate care or training in adult primary care. Therefore, general internal medicine has enjoyed a resurgence, and the primary care internal medicine concept has developed. Primary care internal medicine is equated with general internal medicine by some physicians[29] who thus support the notion that there should be no dichotomy in residency training between the two.[30,31] Both share the same indispensable forte—adult diagnostic acumen in the true Oslerian sense. Sir William stated it clearly in his *Aphorisms:* "There are, in truth, no specialties in medicine, since to know fully many of the most important diseases, a man must be familiar with their manifestations in many organs." Closer inspection, however, shows distinct differences between general internists and primary care internists, especially in initial training (Figure 1). In addition to training in all areas of internal medicine, primary care internists must also, by definition, be prepared to provide first-contact care for adult patients; this entails training in several non-internal medicine subspecialties. This is summarized elsewhere[24,31] and involves extensive exposure to those conditions and diseases of dermatology, ear, nose and throat, ophthalmology and gynecology commonly seen in private practice. If a family physician referring a patient with severe congestive heart failure to a cardiologist is guilty of fragmentation of care, a general internist is just as guilty when referring a patient to an ophthalmologist for contact-lens corneal abrasion. Moreover, a primary care internist is more likely to address the psychosocial aspects of illness, considering office and inpatient psychology a pertinent area of concern that has

a valid literature base.[32] Since Engle's seminal emphasis on psychosocial aspects of illness,[33] much has been written about psychologic training, but recent evidence suggests that deficiencies persist.[34,35]

Internal medicine subspecialists are seldom given training in rendering first-contact primary care. Mendenhall and associates[36] and Aiken and colleagues[37] have noted the large numbers of internal medicine subspecialists who are assuming primary patient care responsibility. But subspecialist priorities and training tend to encourage increased consultations and fragmentation of care in office gynecologic and other common noninternal medicine outpatient problems. Recent sources[21,38] have noted the importance of *comprehensiveness*—that is, the ability to treat over 90 percent of presented problems without referral—as a distinguishing attribute of good primary care.

All of the above has prompted the appearance of primary care internal medicine training programs in many medical centers. If this primary care emphasis is valid, and if one believes that a major onus for redressing physician manpower imbalance must rest with internal medicine,[8] then internal medicine must seek to heal its split in a manner acceptable to both subspecialists and primary care-oriented internists. As President Reagan seeks to trim federal grants to separate primary care tracks, practitioners in internal medicine should emphasize resynthesis, rather than support for continued separation.[39] Although many proposed solutions concern postresidency training,[40] changes must occur well before this, as the forces that mold internists are operative throughout residency and even medical school. Changes meant to restrict subspecialty positions probably will fail. Changes that make primary care and general internal medicine attractive are more likely to succeed. In 1974, 20 percent of graduating medical students were applying for family practice or primary care training,[9] and this number is growing. It is not that primary care is inherently unappealing, but that it is relegated to second-class status by current internal medicine residency and fellowship training.

Some Solutions

Changes in Residency Training

In this era of new internal medicine residency tracks, it is easy to jump from perceived need to implied solution without questioning previous assumptions based on currently limited data. Are three (or more) years necessary to train a general internist, and what should be the makeup of these years? These questions will be addressed in more detail later and require defined residency objectives and competency measurement, information that just now is beginning to appear in volume. For now, the general consensus seems to be that at least three years are necessary for acquisition and consolidation of general internal medicine knowledge.[41] Moreover, most internists who have completed a fourth year of chief residency would likely assert that this additional time was extremely valuable for further consolidation of knowledge and concepts. Until more data are forthcoming, some comments can be made on the changing residency picture.

At the outset, it should be clarified that medical residency is meant to train general internists in diagnosis and treatment, not to train minisubspecialists. Currently most large academic center medical school departments are subspecialty dominated, and residency training programs, especially the last year, are subspecialty oriented. Indeed, in many cases residents may be said to exist for the subspecialty programs, rather than vice versa. It logically follows that general and primary care internists should play an integral part in residency training programs. All too often this is not the case. Generalists are a distinct minority in a self-defeating system that does not create more of their kind.[42] Indeed, it is hard for the general internist to find a research and publication niche in the current university setting.[43]

An internal medicine residency should include aspects of both classical internal medicine training programs and the new primary care tracks. This would involve the following changes in internal medicine residency training, which might be adopted nationwide:

First, throughout the three years of residency there should be a thread of outpatient continuity of care best organized along the team concept prevalent in many private practice groups. These teams would ideally consist of residents of all three years, and patients in the group would have primarily individual, but also group coverage, identity. Although clinical time would be increased throughout the three-year residency, the third-year practice team members would spend the bulk of their time in this mode. Hurst,[12] Goroll and

associates[42] and others have described such innovations in isolated primary care tracks. The first two years of residency would otherwise remain much the same as currently constituted—that is, intense inpatient, emergency room and intensive care unit experience—but with all resident practice teams represented and, therefore, with continuity of outpatient-inpatient care assured.

Second, the third year of internal medicine residency should be reorganized along general internal medicine lines with longitudinal care capabilities. Currently, this third year usually consists of a series of subspecialty "mini-fellowships," often emphasizing procedures (for example, flexible gastroduodenoscopy) that will not be done subsequently by generalists, and certainly not by those entering another subspecialty later in training. In a subspecialty rotation, in-hospital patients are seen who often have been seen by one or more physicians already and represent no special diagnostic problems other than the need for a specific procedure. Subspecialty expertise could instead be gained through patient contact in resident group practice general medicine clinics with resident team continuity assured if the patient needs to be admitted to hospital. Any subspecialist procedures not taught during the first two years and felt necessary for a general internist (bone marrow biopsy or diagnostic liver biopsy) could be taught during this third year by subspecialist postgraduate fellows who would also appropriately cover procedure-oriented in-hospital subspecialty consultations. As the revised third year would consist of more time in the outpatient clinics, a rigorous intensive care unit "refresher" rotation of one or two months could be planned at an appropriate time during the final year. This is entirely consistent with the general internist's role in the care of critically ill patients.[44]

Third, the last residency year should contain extensive consultative experience. Practitioners in general surgery, obstetrics, gynecology, urology and other specialties would be urged to obtain general medicine consultation before any opinion from an internal medicine subspecialist. This function, now often performed by chief residents, provides invaluable experience in diagnostic and referral patterns.

As described, the final year of medical residency would no longer be subspecialist dabbling, but would represent further intense general training on both an inpatient and outpatient basis, laying the framework for later training and research, be it in a subspecialty or primary care.

Changes in Fellowship Training

Altered residency training programs provide only a partial solution to training primary care internists on a large scale. Internal medicine needs a new subspecialty, not another splitting or reductionistic subspecialty, but an integrative, holistic one—that of primary care.

As noted earlier, if three years are desirable for standard general internal medicine training, how much time is ideal, especially if a distinction is made between general internal medicine and primary care internal medicine and new outpatient material is added? Again, some past assumptions may not be justified. Barondess[45] has advocated general internal medicine fellowships of two additional years, with the main justification being that this period is "reasonable" and similar to classical subspecialty fellowships. Although some feel that adequate non-internal medicine clinic training can be provided in the basic three-year residency program, the consensus of those prominent in internal medicine seems to favor at least one extra year,[46] especially if new material is taught. Specific formulation of primary care training objectives and competency measurements, however, has been lacking. One of the few efforts to define comprehensive objectives for teaching such material has resulted in the 300-page curriculum for the clinical education and training of physicians in primary care medicine formulated by Hatem and co-workers.[31] Time requirements needed to meet these objectives in an internal medicine context remain unclear, but the amount of material seems to support the consensus for one or, ideally, two extra years of training for the primary care internist.

In a separate fellowship, appropriate training for primary care internists can be continued. Although such fellowships have been suggested and started, this concept should be formalized nationally under the aegis of the American Board of Internal Medicine (ABIM). A separate subspecialty board and national examination in primary care internal medicine would then follow. This proposal would do much to solve the dilemma facing internal medicine.

In a subsequent one or two years of primary care internal medicine fellowship, intensive training in non-internal medicine subspecialties could

be effected, in addition to ongoing internal medicine training and teaching. As in other subspecialty fellowships, research and publication would be undertaken, for example on critical health care and teaching problems in medicine.[47]

Primary care fellows could also assume the functions of the chief resident. The chief-resident concept has survived over the years because of the necessary functions performed in a teaching program and the prestige of being selected; but from an individual career viewpoint, it is often a dead-end year. A chief resident's enthusiasm and ward presence often wane as the house staff gains experience and as the chief resident travels for interviews and generally prepares for his or her subsequent career as a fellow in a chosen subspecialty. The stated goal, that of making "the trainee a better physician,"[12] is certainly valid, but what are the similar opportunities for internal medicine residents *not* chosen as chief resident? With primary care fellowships, the goals and functions of the chief residency would integrate smoothly into the total internal medicine academic structure.

Moreover, by providing full training and academic credibility to the primary care internist, primary care fellowships would assure an influx of internists into primary care, thus providing role models in practice and academic settings. Academic internal medicine will be better able to create viable divisions of primary care internal medicine coequal with other subspecialty divisions and responsible for providing organization and appropriate ward attendings for the residency program. All internists are historically familiar with ward attending physicians who, although good in their subspecialty, were less than ideal as general medicine attending physicians.

Finally, a separate two-year fellowship in primary care internal medicine would end the sham of the current internal medicine boards. It has been stated recently that the internal medicine board examination has been changed to emphasize general internal medicine.[48] However, having passed the 1978 internal medicine specialty boards, the author noted only a few questions on abstruse problems in dermatology and psychiatry, and little coverage of urologic, ophthalmologic, or ear, nose and throat problems seen in private practice. No questions at all addressed the field of office gynecology. A separate subspecialty board examination in primary care internal medicine would cover not only internal medicine problems, but also continuity of care involving all internal medicine and other office subspecialties in an outpatient and inpatient context.

For the reasons just stated, an internist who is board certified in general internal medicine may be left somewhat in limbo. As currently trained, an internist fresh from a standard three-year residency and general board certification is not ideally trained to render true primary care to adult patients. For an internist entering a classic internal medicine subspecialty fellowship, however, current general board certification is adequate and could stand as now formulated. Barondess[45] has suggested two graded internal medicine board examinations, one for practicing general internists and a more difficult version for academic internists. It is unclear what new information would be in this test that would not be covered in an appropriate subspecialty board examination or be available from an appropriate consulting subspecialist in either a patient care or academic setting. Dr. Daniel Federman remarked on this quandary in 1977[49] and could not resolve it, as he sought no distinction between primary care internal medicine and general internal medicine. If two general board examinations are logical, why not then initiate two separate examinations in, for instance, cardiology—a simple version for a practicing cardiologist and an advanced version for the academic cardiologist?

Reasons exist, therefore, for making primary care internal medicine a discipline separate from initial general medicine certification. Though full division is desirable, some people may favor a modified separation. Petersdorf[8] and ABIM[40] have considered and rejected a four-year training requirement that would produce a generalist with a subspecialty "hobby" (Figure 1). Although subspecialty dabbling is probably self-defeating and dangerous in classic internal medicine subspecialties, this system could be modified in the opposite direction to produce general internists with a "minor" (extra year) in primary care. After four years, the candidate would qualify for a single extended examination covering internal medicine and other office subspecialties.

Conclusions

Admittedly some of the above concepts are not new. The American Board of Internal Medicine and the Federated Council for Internal Medicine have proposed broad theoretical guidelines[50] for support of general internists, but specific unifying

proposals have received insufficient national discussion, especially in light of currently proposed budget cuts.

Although the opening quotation from Sir William Osler is not as true now as in 1897, his observations on internal medicine as a vocation should serve as an appeal to review basic but forgotten precepts that have guided internal medicine in the past.

REFERENCES

1. Alpert JJ, Charney E: The Education of Physicians for Primary Care, DHEW Pub No (HRA) 74-3113. US Dept of Health, Education and Welfare, 1974

2. Johnson KG, Deuschle KW: Primary care: Challenge to academic institutions. Mt Sinai J Med NY 45:591-671, Sep-Oct 1978

3. Hudson JI Nourse ES (Eds): Perspectives in primary care education—Part II. J Med Educ 50:9-253, Dec 1975

4. McDermott W: General medical care—Identification and analysis of alternative approaches. Johns Hopkins Med J 135: 292-321, Nov 1974

5. Schroeder SA, Werner SM, Piemme TE: Primary care in the academic medical centers: A report of a survey by the AAMC. J Med Educ 49:823-833, Sep 1974

6. Berliner RW: Medical education and scholarly inquiry, *In* Beyond Tomorrow—Trends and Prospects in Medical Science. New York, Rockefeller Univ Press, 1977, pp 41-44

7. Rogers DE, Blendon RJ: The academic medical center—A stressed American institution. N Engl J Med 298:940-950, Apr 27, 1978

8. Petersdorf RG: The doctors' dilemma. N Engl J Med 299: 628-634, Sep 21, 1978

9. Janeway CA: Family medicine—Fad or for real? N Engl J Med 291:337-343, Aug 15, 1974

10. Petersdorf RG: Health manpower: Numbers, distribution, quality. Ann Intern Med 82:694-701, May 1975

11. Endicott KM: The distribution of physicians geographically and by specialty. Read before the Institute of Medicine, National Academy of Sciences, May 8, 1974

12. Hurst JW: The training of primary care internists and primary care subspecialists at Emory University School of Medicine. Am J Med 60:603-613, May 10, 1976

13. Eisenberg JM: Residencies that emphasize primary care. Forum on Med, Aug 1978, p 52

14. McWhinney IR: Family medicine in perspective. N Engl J Med 293:176-181, Jul 24, 1975

15. Spitzer WO: The intellectual worthiness of family medicine. Pharos 40:2-13, 1977

16. Reynolds RE: Primary care, ambulatory care, and family medicine: Overlapping but not synonymous. J Med Educ 50:893-895, Sep 1975

17. Pellegrino ED: The generalist function in medicine. JAMA 198:541-545, Oct 1966

18. AMA House of Delegates finally classifies primary care. AAFP Reporter 4:1-16, Jan 1977

19. Tusken R: Report from the executive director. AAFP Reporter 2:6, Jul 1975

20. Director-General of the World Health Organization and Executive Director of the United Nations Children's Fund: Primary Health Care. Geneva, World Health Organization, 1978

21. Institute of Medicine: Primary Care in Medicine: A Definition, IOM publication No. 77-03. Washington, DC, National Academy of Sciences, Jun 1977

22. Aiken LH: Physicians: How many do we need? Ann Intern Med 93:135-136, Jul 1980

23. Martin LR: Is family medicine becoming an ambulatory care specialty? Semin Fam Med 1:165-170, Aug 1980

24. Deller JJ Jr: On the training of the internist for the practice of internal medicine—Present concepts. Ambulatory Internal Medicine Care Symposium, Department of Medicine, Letterman Army Medical Center, 1976

25. Albert JJ, Kosa J, Haggerty RJ, et al: The types of families that use an emergency clinic. Med Care 7:55-61, Jan-Feb 1969

26. Oppenheim M: Healers. N Engl J Med 303:1117-1120, Nov 6, 1980

27. Relman AS: Who will train all those primary care physicians? N Engl J Med 299:652-654, Sep 21, 1978

28. Martin LR: From . . . the President. Fam Med Times 10:2, Feb 1978

29. Saunders JH: The general internist—A potential solution to the health care provision problem. Arch Intern Med 137:1274-1279, Sep 1977

30. Griner PF: Training of the general internist—Different approaches. Arch Intern Med 137:1291-1298, Sep 9, 1977

31. Hatem CJ, Lawrence RS, Arky RA: A Curriculum for the Clinical Education and Training of Physicians in Primary Care Medicine. Boston, Mount Auburn Hospital, Jun 1978

32. Young LE: Changes in the postdoctoral education of internists. Ann Intern Med 83:728-730, Nov 1975

33. Engle GL: The need for a new medical model: A challenge for bio-medicine. Science 196:129-136, Apr 8, 1977

34. May S: On my medical education: Seeking a balance in medicine. Read before the University of California, San Francisco, Senior Class, Alumni and Faculty, May 1978

35. Brody DS: Physician recognition of behavioral, psychological, and social aspects of medical care. Arch Intern Med 140:1286-1289, Oct 1980

36. Mendenhall RL, Tarlov AR, Girard RA, et al: A national study of internal medicine and its specialties: II. Primary care in internal medicine. Ann Intern Med 91:275-287, Aug 1979

37. Aiken LH, Lewis CE, Craig J, et al: The contribution of specialists to the delivery of primary care—A new perspective. N Engl J Med 300:1363-1370, Jun 14, 1979

38. Fleming TC: The public speaks of primary care. Postgrad Med 66:33-34, Nov 1979

39. Byyny RL: SREPCIM Newsletter, Mar 20, 1981

40. Reitemeier RJ, Benson JA Jr: Two views of 'the doctors' dilemma'—As the Board sees it (Sounding Boards). N Engl J Med 299:1308-1309, Dec 7, 1978

41. Tumulty PA: The general internist—A perspective. Arch Intern Med 137:1277-1279, Sep 9, 1977

42. Goroll AH, Stoeckle MD, Goldfinger SE, et al: Residency training in primary care internal medicine—Report of an operational program. Ann Intern Med 83:872-877, Dec 1975

43. Dillard RA: Primary-care manpower: The doctor's dilemma (Letter). N Engl J Med 299:1310, Dec 7, 1978

44. Federated Council for Internal Medicine: The internist (specialist in internal medicine). Forum on Med, Nov 1980, pp 732-734

45. Barondess JA: The training of the internist with some messages from practice. Ann Intern Med 90:412-417, Mar 1979

46. Williams HE (Ed): Training of the general internist—Report of discussion groups. Arch Intern Med 137:1303-1304, Sep 9, 1977

47. Williams KN, Brook RH: Research opportunities in primary care. Mt Sinai J Med 45:663-672, Sep-Oct 1978

48. Petersdorf RG: Evaluation of the general internist. Arch Intern Med 137:1305-1310, Sep 9, 1977

49. Gardner LB (Ed): The role and training of the general internist—Panel discussion. Arch Intern Med 137:1330-1334, Sep 9, 1977

50. Federated Council for Internal Medicine: Statement of manpower. Arch Intern Med 90:108-109, Jan 1979

Refer to: Geyman JP: Training for primary care: A family practice perspective (Editorial Comment). West J Med 136: 83-84, Jan 1982

EDITORIAL COMMENT

Training for Primary Care: *A Family Practice Perspective*

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IN HIS ARTICLE "Training the Internist for Primary Care" in this issue, Dr. Kenneth Kurtz proposes the addition of up to two years of primary care fellowship training to the traditional three-year general medicine residency program. He sees this change as better meeting the educational needs of primary care internists, while preserving their consultant role. Recommendations are made for widespread extension of this concept on a national basis. The argument is buttressed by undocumented statements concerning the "limitations" of family practice, including the alleged superficial nature of clinical training, fragmentation of care because of resultant referrals and questionable role in the case of patients who are very sick.

The article at once raises many issues relating to graduate medical education and the primary care specialties, and it is not possible to address them all in a brief editorial commentary. Two basic problems, however, warrant comment here: (1) the overstated case for the content and outcome of the proposed graduate training of primary care internists and (2) the inaccurate portrayal of the role of family practice as a primary care discipline.

First, with regard to training of primary care internists, this proposal requires an unnecessarily long residency program and perpetuates the basic indecision and tension between consultant and primary care roles of the internists so trained. The proposal assumes that the traditional three-year general medicine residency is a necessary initial requirement for primary care internists, despite its emphasis on the episodic care of selected patients in hospital and in specialty clinics. A restructured three-year residency program should provide ample time if the overriding goal is to train internists who will provide primary care. There is no evidence to suggest that extending the program to four or five years will more effectively prepare internists with the knowledge, skills and commitment required for primary care practice. Residents are not likely to be attracted in large numbers to such extended programs, only to be certified in primary care internal medicine. There is little reason to expect that such an approach would arrest the current trend to substantial subspecialty practice of graduates.[1,2] In addition, internists with this kind of training will probably not compete effectively in most communities for subspecialty referrals in the presence of an undisputed projected surplus of consultants in all of the medical subspecialties. Some studies have already shown that general and family physicians refer most commonly to the surgical specialties and medical subspecialties, not to general internists or general pediatricians.[3,4] Dr. Kurtz's case for primary care internists as a major need in rural areas of Nevada and elsewhere is unpersuasive because it is widely acknowledged among physicians practicing in rural areas that a broader range of competencies is required and that coverage problems usually preclude a multispecialty approach. National extension of Dr. Kurtz's proposals as the dominant form of primary care in this country necessarily commits American families to fragmentation of care among at least three physicians (internist, pediatrician and obstetrician-gynecologist) merely to manage their everyday illnesses and problems.

Second, several of Dr. Kurtz's representations

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about family practice bear comment. After more than ten years of experience, there is ample evidence that three-year family practice residencies provide their graduates with the necessary breadth and depth of clinical competencies to effectively manage most of their patients' health problems, both in and out of hospital. Recent graduate follow-up studies have shown that more than 90 percent of these graduates hold hospital privileges in pediatrics, medicine and family practice, including intensive care unit privileges in most instances. About two thirds of family practice residency graduates provide obstetric care. Approximately 96 percent of graduates nationally are satisfied with their hospital privileges, and most are well satisfied with their overall professional lives.[5] Referral rates among family physicians generally range between 2 percent and 4 percent of patient visits. In the majority of consultations and referrals, family physicians share the responsibility for ongoing care of the patient with the consultants.[3,4] Several studies have shown the quality of care provided by family physicians to be comparable with that provided by other specialists for similar clinical problems.[6-8] A high level of interest has been sustained among medical students for the still-limited number of family practice residency positions that are available. In addition, a number of patient surveys have shown consistently high levels of satisfaction with services provided.[9,10]

This country's present pluralistic approach to primary care is likely to continue in the future, and the three primary care disciplines (family medicine, general internal medicine and general pediatrics) share some similar goals and problems in their efforts to best serve the public interest. As comparatively broad-based specialties, each necessarily draws some of its teaching from other clinical disciplines. Rather than the either-or approach implied in Dr. Kurtz's paper, these three disciplines could usefully collaborate in such areas as curriculum development, program evaluation, research and resolution of common problems such as current disincentives within the reimbursement system that limit many needed primary care services. If the nation's needs for primary care are to be adequately met, graduate training in each of these specialties must be carefully tailored to their future primary care roles, not merely provided on an add-on basis to established programs with other goals.

REFERENCES

1. Wechsler H, Dorsey JL, Bovey JD: A follow-up study of residents in internal medicine, pediatrics and obstetrics-gynecology training programs in Massachusetts—Implications for the supply of primary-care physicians. N Engl J Med 298:15-21, Jan 5, 1978

2. Lee PR: Graduate medical education 1976? Will internal medicine meet the challenge? (Editorial). Ann Intern Med 85: 250-253, Aug 1976

3. Metcalfe DHH, Sischy D: Patterns of referral from family practice. J Fam Pract 1:34-38, Aug 1974

4. Geyman JP, Brown TC, Rivers K: Referrals in family practice: A comparative study by geographic region and practice setting. J Fam Pract 3:163-167, Apr 1976

5. Geyman JP (Ed): Profile of the residency trained family physician in the United States, 1970-1979. J Fam Pract 11:715-784, 1980

6. Garg ML, Mulligan JL, Gliebe WA, et al: Physician specialty, quality and cost of inpatient care. Soc Sci Med (In press)

7. Ely JW, Ueland K, Gordon MJ: An audit of obstetric care in a university family medicine department and an obstetrics-gynecology department. J Fam Pract 3:397-401, 1976

8. Phillips WR, Rice GA, Layton RH: Audit of obstetrical care and outcome in family medicine, obstetrics and general practice. J Fam Pract 6:1209-1216, 1978

9. Schroeder RE: Satisfaction of patients in two Air Force family practice programs. J Fam Pract 4:731-733, Apr 1977

10. Freer JA, Burdette JA, Crocker MA: Patient satisfaction with a model family practice center. J Fam Pract 4:971, May 1977

Refer to: Martin AR: Primary care training: How much, for whom? (Editorial Comment). West J Med 136:85, Jan 1982

EDITORIAL COMMENT

Primary Care Training: *How Much, for Whom?*

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SHOULD PRIMARY CARE be provided by the broad specialty of family practice or by the more specialized approaches of internal medicine and pediatrics? This is one of the questions raised by Dr. Kenneth Kurtz in a Medical Education article in this issue. It is likely that for the foreseeable future both approaches are needed to provide an adequate number of physicians trained to deliver primary care.

In 1975 the Coordinating Council on Medical Education estimated that 50 percent of medical school graduates would need to enter the primary care specialties of family practice, internal medicine and pediatrics to provide a sufficient number of primary care physicians.[1] Family practice constitutes only 15 percent of total residency positions. Internal medicine, which receives 35 percent of medical school graduates, still is the largest source of physicians potentially available for primary care.[2] The problem, as Dr. Kurtz points out, is that as many as 70 percent of physicians completing an internal medicine residency enter subspecialty training.[2] Though many of these subspecialists will end up providing primary care,[3] most of them, and in fact most general internists, do not receive training for the types of problems seen in primary care practice.

It has been assumed that traditional internal medicine training based principally in a hospital prepared residents for the practice of general internal medicine. In reality, many other skills are needed. Management of medical problems is not the same outside of hospital. In addition, skills are needed in the areas of dermatology, gynecology, neurology, ophthalmology, orthopedics, otolaryngology and surgery. Primary care physicians should be skilled behavioral scientists and should know something about the principles of clinical epidemiology, disease prevention, resource utilization and rehabilitation. Family practice and primary care internal medicine programs provide this type of training, but traditional internal medicine residencies do so only to a limited degree. The traditional half-day per week "in the clinic" has not been a highly valued experience.

How then do we provide more physicians with the skills they will need in practice? Perhaps it is time for traditional internal medicine programs to consider including more primary care training in their residencies. A more extensive and structured experience with outpatient care would allow the standard training to include content relevant to the care of patients in and out of the hospital. Despite the concern alluded to by Dr. Kurtz, competence in caring for acutely ill patients in hospital and those seen in office practice can be developed in three years. The need for three full years of in-hospital training, with a fourth year to develop skills in caring for ambulatory patients, has not been felt necessary by those responsible for primary care internal medicine programs. The rotations directed at caring for acutely ill patients have been preserved. Ambulatory time is created by sacrificing in-hospital subspecialty rotations that focus on referral problems less relevant to primary care physicians. Additional subspecialty skills for those who desire them can be obtained in postresidency fellowship. In this way all internists will be better prepared for the primary care they are more likely to provide.

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REFERENCES

1. Coordinating Council on Medical Education: Physician Manpower and Distribution: The Primary Care Physician. Chicago, Coordinating Council on Medical Education, 1975

2. Petersdorf RG: The doctors' dilemma. N Engl J Med 299: 628-634, Sep 21, 1978

3. Aiken LH, Lewis CE, Craig J, et al: The contribution of specialists to the delivery of primary care: A new perspective. N Engl J Med 300:1363-1370, Jun 14, 1979

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Information

Probability of Coronary Heart Disease Developing

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IN THE FRAMINGHAM STUDY a sample of adults has been followed since 1948 in order to investigate the development of cardiovascular disease. The sample is composed of several thousand men and women who live in Framingham, Massachusetts. Biennial clinical examinations provide information about the characteristics of persons in the study both before and after the onset of cardiovascular disease. The investigators in the Framingham study have sought to determine those characteristics that are associated with subsequent development of heart disease.

The data collected provided the basis for estimating values in multiple logistic functions using the Duncan-Walker method. A multiple logistic function yields a person's estimated risk of disease given his or her values on certain clinical characteristics called risk factors.

In 1973 the American Heart Association published the *Coronary Risk Handbook*[1] based on a particular set of these logistic functions. This pamphlet was designed for easy use by physicians and consists of nearly 100 tables. A physician can determine a patient's risk that heart disease will develop within the next six years by locating on the pertinent table risk factors for the patient's age, systolic blood pressure, serum cholesterol, cigarette smoking, presence or absence of glucose intolerance and presence or absence of left ventricular hypertrophy shown on an electrocardiogram (ECG).

From the Division of Biostatistics, Stanford University Medical Center, Stanford, California. Ms. Brittain is now affiliated with the University of North Carolina School of Public Health, Chapel Hill.

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The charts presented in Figures 1 and 2 were designed to be used in place of the tables in the *Coronary Risk Handbook*. They are less cumbersome to use and also indicate the relative importance of the factors. The charts and the handbook are mathematically equivalent as they are both derived from the same set of multiple logistic functions. However, the chart probabilities may be slightly less accurate than those in the handbook.

Definition of Risk Factors

The following definitions of the risk factors are taken from the *Coronary Risk Handbook:*

- *Systolic blood pressure* (SBP)—given in millimeters of mercury. Casual pressure taken with the patient seated.
- *Serum cholesterol* (chol)—given in milligrams per deciliter as measured by the Abell-Kendall method. Correction is necessary if another laboratory method is used.
- *Left ventricular hypertrophy* (LVH)—as evaluated by ECG, is determined by the finding of tall R waves in leads reflecting potentials from the left ventricle, accompanied by S-T depression or T-wave inversion. Other ECG abnormalities (including intraventricular conduction disturbance, nonspecific S-T depression and T-wave inversion abnormalities) carry an excess risk of a similar magnitude.
- *Smoking* (cig)—refers to current cigarette-smoking habit. The charts do not take into account intensity of smoking habit (packs per day per number of years) and contrast only smokers versus nonsmokers.
- *Glucose intolerance* (glu)—as evidenced by diabetes, trace or more of sugar in the urine, or a casual (nonfasting) whole blood glucose level of 120 mg per dl or greater.

Examples

For the given example, Table 1 presents a calculation of the probability of coronary heart disease developing in men according to the charts, and the associated probability listed in the *Coronary Risk Handbook*. The calculation for women is displayed in Table 2.

Comments

The regression coefficient for cigarette smoking in women is so small that smoking adds no points

ABBREVIATIONS USED IN TEXT

ECG = electrocardiogram
HDL = high-density lipoproteins
SBP = systolic blood pressure

to a woman's risk score. This result may be illuminated somewhat by examination of the relationship of smoking to various forms of coronary heart disease. Women with angina pectoris constitute most of the women who are designated as having coronary heart disease. Data from the Framingham study do not indicate increased incidence of angina pectoris among women who smoke. Trends in the data suggest, however, that smoking may be associated with an increased incidence of myocardial infarction in women 45 to 64 years old.[2] Thus the lack of points for smoking reflects its nonassociation with angina and may mask its possible association with the more serious condition of myocardial infarction. Had analogous charts been compiled to compute the probability of a myocardial infarction, it would be expected that one or two points might have been assigned to cigarette smoking.

To understand further why there are no points assigned to cigarette smoking, it is important to realize that this simply indicates that knowledge of the patient's smoking habit in the presence of knowledge of the other risk factors does not aid in the *prediction* of heart disease. While this may be due to the lack of a relationship between smoking and heart disease, such is not necessarily the case as illustrated by the following situation. Suppose cigarette smoking, acting alone or in combination with some other factor, has a deleterious effect on one or several of the other risk factors. Under this circumstance, the impact of smoking may be expressed almost entirely through the action of those factors affected by smoking. Thus

Calculation of Probability

Points												
SBP	100	110	120	130	140	150	160	170	180	190	200	
CIG	No				Yes							
LVH	No						Yes					
GLU	No		Yes									

Enter Points for

\+ Systolic Blood Pressure
\+ Cigarette Smoking
\+ Left Ventricular Hypertrophy
\+ Glucose Intolerance
\+ Age/Serum Cholesterol
= Total Points → Probability

Chol	Age 36	38	40	42	44	46	48	50	55	60	65	70
165	3	6	9	11	14	16	18				27	27
180		8	10	13	15	17				25		27
195	7	9		14	16	18			11			
210	8			15	17	19	21					
225	10	12	15		19							
240	11	14	16	18				24				
255	13	15	17	19								27
270	15	17	19	21								26
285	16		20	22								
300	18			23			27					
315	20	22			26	27			30		29	

TP	Prob	TP	Prob	TP	Prob
	.003		.021	35	.13
6	.004	21	.024	36	.14
	.004		.028	37	.16
8	.005		.031		.17
	.006		.035		.19
	006		.040		.21
11	.007		.045		.23
	.008		.050		.25
	.009		.057	43	.28
	.010		.064		.30
	.012		.071		.33
	.013		.080		.36
	.015		.090	47	.39
18	.017	33	.100		.42
19	.019	34	.11	49	.45

Left Ventricular Hypertrophy — as evaluated by electrocardiogram (ECG).

Glucose Intolerance — as manifested by diabetes, or a trace or more of sugar in the urine, or a non-fasting whole blood glucose level of 120 mg% or greater.

Figure 1.—Probability of coronary heart disease developing in six years, men (aged 35-70). (Compiled by Erica Brittain at Stanford University, 1979, from multiple logistic functions in *The Framingham Study.*[2])

the lack of points for smoking should not be viewed as an exoneration of smoking as an agent of coronary heart disease in women.

Since publication of the *Coronary Risk Handbook,* it has been reported that low levels of high-density lipoproteins (HDL) are associated with increased incidence of coronary heart disease. Kannel and associates[3] have proposed a simple way to include HDL in the assessment of coronary risk. There are no Framingham data on HDL for those younger than 50 years, so that the use of this method relies on the assumption that the relationship between HDL and coronary heart disease remains constant regardless of age. If the HDL value is known, determination of the risk of heart disease obtained by the charts can be refined by multiplying this risk by the appropriate "multiplier" listed in Table 3. If the charts assign a 0.14 probability of heart disease developing in a man whose HDL value is known to be 40, a more accurate assessment of his risk is

$$(0.14 \times 1.22) = 0.17.$$

Construction of Charts

The estimated risk is a function of $\Sigma \hat{\beta}_i x_i$ where $\hat{\beta}_i$ is the estimated regression coefficient and x_i is the value of the i-th risk factor in the logistic function

$$\text{estimated risk} = \frac{1}{1 + \exp\,(-\hat{\alpha} - \Sigma \hat{\beta}_i x_i)}.$$

The regression coefficients are published in section 27 of *The Framingham Study.*[4]

The objective of the charts is to reproduce $\Sigma \hat{\beta}_i x_i$ with a simple scoring system. This is achieved by assigning points to specified values of risk factors. Points are assigned as follows:

$$\text{point}_i = (\hat{\beta}_i x_i \times \text{scale factor}) - \text{translation factor}_i.$$

The scale factor and translation factors are chosen to give the charts certain desirable properties. Once the point values are obtained, $\Sigma \hat{\beta}_i x_i$ can be expressed as

$$\Sigma \hat{\beta}_i x_i = \frac{\Sigma\,(\text{point}_i + \text{translation factor}_i)}{\text{scale factor}}.$$

Assignment of a point value to a systolic blood

Calculation of Probability

Points	–	–	2	3	4	5	6	7	8	9	10
SBP	100	110	120	130	140	150	160	170	180	190	200
LVH	No			Yes							
GLU	No			Yes							

Note: No points added for Smoking

Enter Points (in gray) for

_____ Systolic Blood Pressure
\+ _____ Left Ventricular Hypertrophy
\+ _____ Glucose Intolerance
\+ _____ Age/Serum Cholesterol
= _____ Total Points → Probability

Chol	Age 36	38	40	42	44	46	48	50	55	60	65	70
165	–	2	4	5	7	9	10	12	15	18	20	21
180	–	3	4	6	8	9	11	12	16	18	20	22
195	2	3	5	7	9	10	12	13	16	19	21	22
210	3	4	6	8	10	–	13	14	17	19	21	22
225	4	5	7	9	10	12	13	15	17	20	21	23
240	–	6	8	10	11	13	14	15	18	20	22	23
255	5	7	9	11	12	13	15	16	19	21	22	23
270	6	8	10	11	13	14	16	17	19	21	23	24
285	7	9	11	12	14	15	16	17	20	22	23	24
300	8	10	12	13	15	16	17	18	21	22	24	24
315	–	11	13	14	15	17	18	19	21	23	24	25

TP	Prob	TP	Prob	TP	Prob
5	.002	17	.014	29	.081
6	.003	18	.016	30	.093
7	.003	19	.019	31	.11
8	.004	20	.022	32	.12
9	.004	21	.025	33	.14
10	.004	22	.029	34	.16
11	.006	23	.034	35	.18
12	.007	24	.040	36	.20
13	.008	25	.046	37	.23
14	.009	26	.053	38	.26
15	.010	27	.061	39	.29
16	.012	28	.071	40	.32

Left Ventricular Hypertrophy — as evaluated by electrocardiogram (ECG).

Glucose Intolerance — as manifested by diabetes, or a trace or more of sugar in the urine, or a non-fasting whole blood glucose level of 120 mg% or greater.

Figure 2.—Probability of coronary heart disease developing in six years, women (aged 35-70). (Compiled by Erica Brittain at Stanford University, 1979, from multiple logistic functions in *The Framingham Study.*[2])

TABLE 1.—*Example Using Chart for Men*

Characteristic	*Value*	*Points*
Systolic blood pressure	150	5
Cigarette smoking	yes	4
Left ventricular hypertrophy	no	0
Glucose intolerance	no	0
Age/serum cholesterol	50/285	27
TOTAL		36

Probability: 0.14
Coronary Risk Handbook probability: 0.134

TABLE 2.—*Example Using Chart for Women*

Characteristic	*Value*	*Points*
Systolic blood pressure	120	2
Left ventricular hypertrophy	no	0
Glucose intolerance	no	0
Age/serum cholesterol	50/210	14
TOTAL		16

Probability: 0.012
Coronary Risk Handbook probability: 0.012 (smoker)
0.012 (nonsmoker)

TABLE 3.—*Multiplier for High-density Lipoprotein Cholesterol Level**

High-density Lipoprotein Cholesterol	*Men mg/dl*	*Women mg/dl*
30	1.82	....
35	1.49	....
40	1.22	1.94
45	1.00	1.55
50	0.82	1.25
55	0.67	1.00
60	0.55	0.80
65	0.45	0.64
70	....	0.52

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pressure of 140 mm of mercury is used for illustration. The scale factor 8.036 is chosen because $\hat{\beta}$ for SBP is $0.0124 = (10 \times 8.036)^{-1}$. This produces a one-point increase for each added 10 mm of systolic blood pressure. The translation factor is chosen to be 10 so that a blood pressure of 100 would correspond to 0 points:

$$\text{point} = [(0.01244 \times 140) \times 8.036] - 10 = 14 - 10 = 4.$$

Thus a systolic blood pressure of 140 is assigned 4 points.

A common scale factor must be used for all risk factors. It was felt that choosing a scale factor based on systolic blood pressure gave the most pleasing presentation.

Summary

Based on the multiple logistic functions estimated from the Framingham study data, charts are compiled for calculating the probability of coronary heart disease developing in six years by men and women.

REFERENCES

1. Coronary Risk Handbook—Estimating Risk of Coronary Heart Disease in Practice. New York, American Heart Association, 1973

2. Shurtleff D: The Framingham Study—An Epidemiological Investigation of Cardiovascular Disease. Section 30: Some Characteristics Related to the Incidence of Cardiovascular Disease and Death: Framingham Study, 18-year Followup. Dept. of Health, Education and Welfare (DHEW) publication. US Government Printing Office, 1974

3. Kannel WB, Castelli WP, Gordon T: Cholesterol in the prediction of atherosclerotic disease—New perspective based on the Framingham Study. Ann Intern Med 90:85-91, Jan 1979

4. Gordon T, Sorlie P, Kannel WB: The Framingham Study, An Epidemiological Investigation of Cardiovascular Disease. Section 27. Coronary Heart Disease, Atherothrombotic Brain Infarction, Intermittent Claudication—A Multivariate Analysis of Some Factors Related to Their Incidence: Framingham Study, 16-year Followup. DHEW publication. US Government Printing Office, 1971

in memoriam

California Medical Association

BEGGS, A. FRANKLIN, Long Beach. Died August 25, 1981, aged 91. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1925. Licensed in California in 1925. MD degree from California College of Medicine, 1962. Dr. Beggs was a member of the Los Angeles County Medical Association.

COOK, EDWARD WILLIAM, San Anselmo. Died September 22, 1981, in San Anselmo of cancer, aged 60. Graduate of the Stanford University School of Medicine, Palo Alto, San Francisco, 1946. Licensed in California in 1946. Dr. Cook was a member of the Marin Medical Society.

ENOS, JOSEPH B., Los Altos. Died March 19, 1981, aged 89. Graduate of the Oakland College of Medicine and Surgery, Oakland, California, 1920. Licensed in California in 1920. Dr. Enos was a retired member of the Alameda-Contra Costa Medical Association.

FRASER, ALFORD VANCE, Los Angeles. Died August 24, 1981, aged 73. Graduate of the Dalhousie University Faculty of Medicine, Halifax, 1932. Licensed in California in 1937. Dr. Fraser was a member of the Los Angeles County Medical Association.

GROPER, MORRIS J., San Francisco. Died August 22, 1981, aged 77. Graduate of the McGill University Faculty of Medicine, Montreal, 1930. Licensed in California in 1931. Dr. Groper was a retired member of the San Francisco Medical Society.

HELD, ALBERT H., North Hollywood. Died July 10, 1981, aged 75. Graduate of the Indiana University School of Medicine, Indianapolis, 1930. Licensed in California in 1943. Dr. Held was a member of the Los Angeles County Medical Association.

MACK, MARVIN A., Santa Monica. Died August 5, 1981, aged 73. Graduate of the Creighton University School of Medicine, Omaha, 1932. Licensed in California in 1943. Dr. Mack was a member of the Los Angeles County Medical Association.

PRESTON, WILLIAM DONALD, Orinda. Died September 18, 1981, aged 73. Graduate of the Ohio State University College of Medicine, Columbus, 1936. Licensed in California in 1961. Dr. Preston was a member of the Alameda-Contra Costa Medical Association.

QUINN, JOHN E., Fresno. Died August 13, 1981, aged 62. Graduate of the State University of Iowa College of Medicine, Iowa City, 1952. Licensed in California in 1954. Dr. Quinn was a member of the Fresno-Madera Medical Society.

ROLLERI, THOMAS T., Angels Camp. Died June 10, 1981, aged 70. Graduate of Marquette University School of Medicine, Milwaukee, 1938. Licensed in California in 1938. Dr. Rolleri was a retired member of the Alameda-Contra Costa Medical Association.

TORRANCE, WILLIAM R., Visalia. Died in June 1981, aged 68. Graduate of the University of Southern California School of Medicine, Los Angeles, 1952. Licensed in California in 1952. Dr. Torrance was a retired member of the Tulare County Medical Society.

VIDA, ALEXANDER S., Los Angeles. Died June 27, 1981, aged 67. Graduate of the University of Michigan Medical School, Ann Arbor, 1939. Licensed in California in 1946. Dr. Vida was a member of the Los Angeles County Medical Association.

WARE, ROBERT L., Alameda. Died September 3, 1981, aged 73. Graduate of the Emory University School of Medicine, Atlanta, 1931. Licensed in California in 1959. Dr. Ware was a retired member of the Alameda-Contra Costa Medical Association.

WESSON, MILEY B., San Francisco. Died in June 1981, aged 99. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1910. Licensed in California in 1921. Dr. Wesson was a retired member of the San Francisco Medical Society.

WHISENAND, BENJAMIN M., Martinez. Died April 25, 1981, aged 59. Graduate of the George Washington University School of Medicine, Washington, DC, 1951. Licensed in California in 1952. Dr. Whisenand was a member of the Alameda-Contra Costa Medical Association.

WILCOX, JOHN C., Devore. Died April 6, 1981, aged 71. Graduate of Harvard Medical School, Boston, 1934. Licensed in California in 1938. Dr. Wilcox was a retired member of the Los Angeles County Medical Association.

ZULAUF, WALTER C., Ridgecrest. Died November 9, 1980, aged 87. Graduate of the University of Nebraska College of Medicine, Omaha, 1923. Licensed in California in 1937. Dr. Zulauf was a retired member of the Los Angeles County Medical Association.

New Mexico Medical Society

REYMONT, ANTHONY E., Santa Fe. Died September 30, 1981, in Santa Fe, aged 80. Graduate of Rush Medical College, Chicago, 1926. Licensed in New Mexico in 1939. Dr. Reymont was a retired member of the Santa Fe County Medical Society.

STONE, COY S., Hobbs. Died September 26, 1981, in Hobbs, aged 78. Graduate of Baylor University College of Medicine, Houston, 1929. Licensed in New Mexico in 1930. Dr. Stone was a past president of the New Mexico Medical Society and a member of the Lea County Medical Society.

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DRAMATIC NEW CLINICAL PROOF*

In the treatment of impetigo –

- **100% cure rate with Tegopen®** (cloxacillin sodium)
- **only a 60% cure rate with penicillin V-K**

As seen on admission

After one week of penicillin V-K therapy

Two weeks after initiation of TEGOPEN therapy

Treatment failure was judged to have occurred when lesions increased in size and/or number during the initial week of treatment with penicillin V-K. *No* treatment failures occurred with Tegopen.

*Data on file, Bristol Laboratories.

Brief Summary of Prescribing Information

TEGOPEN®
(cloxacillin sodium)
Capsules and Oral Solution

For complete information, consult Official Package Circular (12) 9/11/75

INDICATIONS

Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed.

IMPORTANT NOTE

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

CONTRAINDICATIONS:

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication

RESULTS OF ORAL THERAPY revealed a high percentage of treatment failures with penicillin V potassium, but *no* failures with Tegopen.

		Given Tegopen® (*cloxacillin sodium*)	Given *penicillin V-K*
Staphylococcus aureus	(78 patients)	39	39
Returned to clinic at one week		29†	38†
Treatment failure at one week		0	18 (47.4%)
Staphylococcus aureus* and *Streptococcus pyogenes	(9 patients)	4	5
Returned to clinic at one week		4	5
Treatment failure at one week		0	2 (40%)
No initial bacterial growth	(14 patients)	9	5
All 14 healed, regardless of which antibiotic was administered.			
Beta-hemolytic *Streptococcus*	(1 patient)	0	1
TOTALS:	**102 patients**	**52 patients**	**50 patients**

†Eleven patients did not return for their one-week checkup. These were all called by telephone, and their families reported the lesions had healed. One patient was dropped from the study, early, because of adverse reaction to medication.

STUDY: DESCRIPTION/PROTOCOL

- 102 nonselected subjects, with initial bacteriology as follows: 77% *Staphylococcus aureus*, 9% mixed *Staphylococcus aureus* and *Streptococcus pyogenes*, and 1% beta-hemolytic *Streptococcus*.‡
- All patients were given randomized therapy—Tegopen capsules or oral solution, or penicillin V-K tablets or oral solution, in recommended dosages according to body weight.
- All patients were evaluated after one week's therapy. If there was no improvement, therapy was switched to the other antibiotic. The "other antibiotic" proved to be Tegopen 100% of the time because no treatment failures had occurred with Tegopen.
- A final assessment of progress was made two weeks after initiation of Tegopen therapy.

‡The remainder, to equal 100%, consisted of 14 patients (13%) who exhibited no initial bacterial growth. These 14 were all healed, whether given Tegopen or penicillin V-K.

TEGOPEN®
(cloxacillin sodium)
–effective therapy for staph infections of the skin and skin structures

WARNING:
Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Safety for use in pregnancy has not been established.

PRECAUTIONS:
The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

ADVERSE REACTIONS:
Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

USUAL DOSAGE
Adults: 250 mg. q.6h.

Children: 50 mg./Kg./day in equally divided doses q.6h. Children weighing more than 20 Kg. should be given the adult dose. Administer on empty stomach for maximum absorption.

N.B. INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

SUPPLIED:
Capsules—250 mg. in bottles of 100, 500 mg. in bottles of 100
Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles

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Bristol Laboratories
Division of Bristol-Myers Company
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(Continued from Page 34)

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Aberdeen, Washington, a coastal community surrounded by mountains, rivers and ocean beaches is the health care center for a population base of 60,000.

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- ENT
- GENERAL SURGEON
- INTERNIST
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This is an immediate opportunity with flexible initial investment. Contact Jim Washam, Habor Medical Surgical Center, Box 482, Aberdeen, WA 98520 or call COLLECT (206) 533-0450. EOE

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Opportunities are available for internists, family practitioners and psychiatrists to work with developmentally disabled people in State residential communities. Locations from Los Angeles to northern California. Challenging and varied cases, congenial professional environment, excellent civil service benefits.

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(916) 322-1221 collect

SITUATIONS WANTED

INTERNIST—35, ABIM Licensed—California with National Board reciprocity. Three years of private consultative practice in critical care medicine. Skilled in right heart catheterization, arterial monitoring and respiratory care. Also two years as director of a large volume Emergency Department. Prefer group or multiple specialty practice. Would consider active emergency practice. Prefer Colorado, Oregon, Washington or California. Box 6271, The Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

NEUROLOGIST with experience in EMG, EEG, CT and Neuromuscular Diseases, seeks solo/group practice opportunity in California. Reply Box 6263, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST (ABIM) with strong Emergency Medicine experience seeks full-time position as Internist or Emergency physician in San Francisco or Seattle area. Reply Jacques Calma, 3830 Carlson Circle, Palo Alto, CA 94306; phone (415) 494-3761.

RADIOLOGIST—Desires locums or permanent position. Contact Anthony Cassens, MD, 2669 Ardsheal Dr., La Habra, CA 90631, (213) 691-1501.

ORTHOPEDIC SURGEON. Age 69. Board certified. Interested in office orthopedics and/or disability examinations. Apply Box 6225, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SITUATIONS WANTED

OB/GYN, 45, Board part one, Spanish speaking, available to join group, association, partnership or established practice in California, prefer coastal areas. Call (714) 963-5919 or (514) 254-8508.

GENERAL SURGEON, 32; trained at major eastern university hospital. Now practicing in southern California. Desire to associate with established individual or group in Los Angeles area or Orange County. Reply Box 6266, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LOCUM TENENS WANTED

FAMILY PHYSICIAN—Board certified, semi-retired wishes part-time position in vicinity San Diego, San Jose or Phoenix. Available July 1, 1982. Reply Box 6264, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CONSCIENTIOUS YOUNG INTERNIST, University trained, seeks locum tenens in Internal Medicine in Bay Area. Available January through June, part or full time. Reply Box 6270, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

DIAGNOSTIC X-RAY, US, NM locum tenens wanted by Diplomate, licensed CA & MT. Box 6261, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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INFORMATION

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LOCUM TENENS WANTED

INTERNIST with young family seeks job-sharing or part-time private association. Desire California suburban to semi-rural area. Write Box 6267, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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IMMEDIATE SALE of otolaryngology practice established 26 years. Fully equipped, furnished in medical professional building, adjacent to hospital in Billings, Montana. Big Sky Country, clean air, lots of outdoor recreation. Real bargain. For details contact M. F. Ross, 1910 Riverview Dr., N.E., Auburn, WA 98002, (206) 939-5609.

GYNECOLOGICAL practice available from retiring specialist. Located eastern slope of Sierra Mountains in a growing community of 35,000 population. Many recreational areas within 30-45 minutes. Write Box 6269, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ORTHOPEDISTS, INTERNISTS, FP/GP, SURGEONS, PEDIATRICIANS, OPHTHALMOLOGISTS, OTHERS. For help in BUYING or SELLING a medical practice, medical building, or arranging an association contact Mary Bradshaw, 21 Altamount Dr., Orinda, CA 94563; (415) 376-0762. Consulting, appraising, partnerships, placement.

PRACTICES WANTED

GASTROENTEROLOGIST interested in buying Internal Medicine Practice in an area with potential to practice Gastroenterology. Call (502) 895-9006 or write A. B. Reddy, MD, 650 Zorn Ave., Louisville, KY 40206.

WISH TO RELOCATE IN SOUTHERN CALIFORNIA. Want to buy well established General Practice with office building as a package. Box 6273, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OFFICES FOR RENT

YUBA CITY, MARYSVILLE—Outstanding opportunity for medical practice. Office in established professional building for lease. Growing area. Reasonable terms. Call Gerald Besson, MD, (408) 739-2249 (O), (415) 948-2043 (H).

MEDICAL SUITE FOR RENT, Established Professional Medical Center, with 2 suites available for rent. Clinic maintains x-ray, laboratory, and pharmacy. Excellent opportunity available at Physicians Medical Center, Indio, CA; (714) 347-1013 or (714) 347-0540.

MEDICAL EQUIPMENT FOR SALE

USED G.E. 200 MA X-RAY MACHINE. Excellent condition. Mounted on wall-bar, with wall mounted cassette holder. $4,500 or best offer. M. Burvant, MD, (916) 933-3450.

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(Continued from Page 23)

March 10—**Hypothyroidism—Unmasked.** LLU. Wednesday. 4 hrs. $30.

March 12-13—**Exercise Stress Testing: Today and Tomorrow.** American College of Cardiology at Memorial Hospital Medical Center, Long Beach. Friday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

March 12-13—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

March 12-14—**Western Institute on Epilepsy.** UCLA at Marriott, Los Angeles. Friday-Sunday. $60.

March 13-20—**Reproductive Endocrinology.** USC at Maui. One week. $395.

March 19-20—**Non-Invasive Cardiology Conference.** Clairemont Community Hospital at Sheraton Harbor Island Hotel, San Diego. Friday-Saturday. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

March 21-24—**Dermatology Consultants' Course.** UCSF at Yosemite. Sunday-Wednesday.

March 22-April 2—**30th Annual Review of Internal Medicine.** USC. 12 days.

March 26-27—**Advances in Heart Disease, Aging, Diabetes and Cancer Research.** See Of Interest To All, March 26-27.

March 26-28—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

March 29-April 2—**Management of Coronary Heart Disease: Medical, Surgical, Exercise.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs.

April-June—**Allergy/Immunology for the Practicing Internist.** UCLA. Wednesday evenings.

April 1-3—**Asthma Update—1982.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Saturday. 19 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 1-4—**Principles in the Practice of Allergic Diseases in Adults and Children.** UCD at Del Monte Hyatt, Monterey. Thursday-Sunday.

April 14—**Cardiology Update 1982.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

April 16-17—**Recent Advances in Renal, Metabolic and Endocrine Disorders.** St. Francis Medical Center at Bonaventure Hotel, Los Angeles. Friday-Saturday. $115. Contact: Allan M. Hoffman, EdD, Dir., Med. Ed., St. Francis Med. Ctr., 3630 E. Imperial Highway, Lynwood 90262. (213) 603-6171.

April 16-18—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

April 23-30—**Dermatology.** UCD. One week.

May 6-7—**Advances in Infectious Diseases.** UCSF. Thursday-Friday. 14 hrs. $170.

May 7-8—**Common Nervous System Pathology Diagnosis and Treatment.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 14 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 7-9—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

May 15-18—**American Thoracic Society—Annual Scientific Meeting.** Bonaventure Hotel, Los Angeles. Saturday-Tuesday. 30 hrs. $35, members; $100, nonmembers. Contact: S. R. Iannotta, Exec. Dir., ATS, 1740 Broadway, New York 10019. (212) 245-8000.

May 17-21—**Advances in Internal Medicine.** UCSF. Monday-Friday. 40 hrs. $375.

May 21-22—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

OBSTETRICS AND GYNECOLOGY

January 31-February 5—**Obstetrics and Gynecology Review and Update.** UCD at Hyatt, Lake Tahoe. Sunday-Tuesday.

February 4-6—**Practical Aspects of Gynecologic Urology, Intraepithelial Neoplasia, Infertility, and Ovum Transplantation.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Saturday. 20 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 6-7—**Los Angeles OB-GYN Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. 10 hrs. $70. Contact: Dir. of Med. Ed., L.A. OB-GYN Soc., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

February 8-12—**37th Annual Postgraduate Assembly.** Obstetrical and Gynecological Assembly of Southern Calif. at Beverly Hilton, Beverly Hills. Monday-Friday. 28 hrs. $375. Contact: Dir. of Med. Ed., OB-GYN Assembly of So. Calif., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 13-20—**Reproductive Endocrinology, Infertility and Contraception.** See Of Interest To All, March 13-20.

March 14-17—**OB/GYN for the Practicing Physician.** UCSF at Yosemite. Sunday-Wednesday.

March 20-24—**American Fertility Society.** See Of Interest To All, March 20-24.

March 27-April 3—**Obstetrics and Gynecology.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 2-3—**27th Annual T. Hart Baker, MD, Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at Hotel del Coronado, Coronado. Friday-Saturday. Contact: Lilia M. Guerrero, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

May 10-12—**Recent Advances in OB/GYN.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 20 hrs. $300.

PEDIATRICS

January 16—**Pediatric Urology-Nephrology Seminar.** Western Section, American Urological Assn., at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Kathy De Santis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

January 31-February 2—**7th Annual Winter Ski and Study Symposium.** Calif. Chap. 2, American Academy of Pediatrics, at Mammoth Mountain. Sunday-Wednesday. Contact: Calif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305.

February 6—**Pediatric Seminar: Congenital Anomalies.** Sutter Community Hospitals at Sutter Memorial Hospital, Sacramento. Saturday. 4 hrs. Contact: (916) 451-8898.

(Continued on Page 42)

Something
happens...

Depressive, anxiety AND somatic symptoms respond rapidly...

without a phenothiazine

A special quality of relief typically comes early to anxious depressed patients treated with Limbitrol. For example, core depressive symptoms—feelings of guilt and worthlessness—often respond within a week. So do insomnia, anorexia, agitation, and psychic and somatic anxiety. And as the anxious depression responds, so, often do the related somatic symptoms—headache, backache, G.I. upset, palpitations.* No less important to the patient's progress is the enhanced compliance that comes with the early sense of well-being.

With Limbitrol, these striking results are obtained without the phenothiazines contained in other dual medications. The causal relationship between the phenothiazines and extrapyramidal side effects, including tardive dyskinesia, is well established. In contrast, the reported incidence of these adverse reactions with Limbitrol or either of its components is rare.

Patients should be cautioned about the combined effects with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car.

*Data on file, Medical Department, Hoffmann-La Roche Inc.

Please see summary of product information on following page.

in moderate depression and anxiety

Limbitrol® 5-12.5 10-25

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

A special quality of relief

ROCHE®

LIMBITROL® TABLETS Tranquilizer–Antidepressant
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Relief of moderate to severe depression associated with moderate to severe anxiety
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction
Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).
***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12.
In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly. Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.
How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50.

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ROCHE PRODUCTS INC
Manati, Puerto Rico 00701

(Continued from Page 39)

February 16-19—**Clinical Investigation.** See Of Interest to All, February 16-19.

February 26-27—**New Directions in Care for the Handicapped Child.** State Dept. of Special Education and Calif. Chap. 1, American Academy of Pediatrics, at Children's Hospital Medical Center of Northern Calif., Oakland. Friday-Saturday. Contact: Peter Miller, MD, Marin Civic Ctr., Rm. 280, San Rafael 94903. (415) 499-6877.

March 11-14—**Combined Southern California Pediatric Postgraduate Program.** Calif. Chap. 2, American Academy of Pediatrics; Los Angeles Pediatric Soc.; Children's Hosp. of Orange Co. and Southwestern Pediatric Soc. at Hilton Riviera, Palm Springs. Thursday-Sunday. Contact: Chalif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305.

March 17-19—**General Pediatrics.** American Academy of Pediatrics at Royal Lahaina Resort, Maui. Wednesday-Friday. Contact: Dept. of Education, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

March 20-25—**American Academy of Pediatrics—Spring Session.** Sheraton Waikiki, Honolulu. Saturday-Thursday. Contact: Dept. of Education, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

April 2-3—**Pediatric Topics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

April 10-17—**Pediatric Emergencies.** See Emergency Medicine, April 10-17.

April 14—**Antibiotic Use in Pediatric Specialty Practice.** LLU. Wednesday. 4 hrs. $30.

April 22-24—**Advances in Pediatrics.** UCSF. Thursday-Saturday. 18 hrs. $250.

April 27-30—**7th Annual Symposium: Care of the Sick Newborn.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Tuesday-Friday. 19 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 1—**Pediatric Ophthalmology for the Primary Care Practitioner.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 6 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 3-7—**12th Annual Review of Pediatrics.** USC. Monday-Friday. 32 hrs. $350.

May 29-31—**Challenges in Pediatrics.** Northern California Chapter, American Academy of Pediatrics, at Monterey. Saturday-Monday. Contact: David A. Zlotnick, MD, 3200 Middlefield Rd., Palo Alto 94306.

PSYCHIATRY

January 21-26—**Psychiatric Symposium.** Continuing Medical Education, Inc., and Western Medical Center at Maui Surf Resort, Maui. Thursday-Tuesday. 24 hrs. Contact: CME, Inc., 2030 E. 4th St., #113, Santa Ana 92705. (714) 547-5186.

January 24-29—**8th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

January 31-February 4—**Mental Research Institute—Winter Seminar.** Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 13-14—**Emotions in Health and Illness: Foundations of Clinical Practice.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday. 12 hrs.

February 19-20—**Heinz Von Foerster on Cybernetics, Language and Understanding.** Mental Research Institute, Palo Alto. Friday-Saturday. 12 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 26-27—**The Use of Drugs in the Treatment of Patients With Psychiatric Disorders.** UCLA at VA Medical Center, Brentwood. Friday-Saturday. 6 hrs. $75.

February 27-28—**Biobehavioral Science for Psychiatrists.** STAN. Saturday-Sunday. 12 hrs. $225.

March 12-14—**Short-Term Dynamic Psychotherapy.** UCSD at Hilton, San Diego. Friday-Sunday. 24 hrs. $275.

March 27—**Reconsiderations of Psychoanalytic Listening.** Southern California Psychoanalytic Society at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Mrs. Carol Ziff, Exec. Sec., So. Calif. Psychoanalytic Soc., 9024 Olympic Blvd., Beverly Hills 90211. (213) 936-2877.

RADIOLOGY AND PATHOLOGY

January 20-22—**9th Annual Course in Genitourinary Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 23 hrs. Contact: Asst. Dir., Center for Health Education, 2801 Atlantic Ave., P.O. Box 1428, Long Beach 90801. (213) 595-3811.

January 29-31—**34th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Diane L. Johnson, L.A. Radiological Society, P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

January 31-February 5—**4th Annual Winter Conference in the High Sierra—OB/GYN Imaging.** American College of Medical Imaging at Sahara, Lake Tahoe. Sunday-Friday. 25 hrs. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

February 3-5—**New Directions in Clinical Laboratory Assays: 4th Immunology Conference.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 18 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

February 10—**Pulmonary Function Tests and Blood Gas Interpretation.** LLU. Wednesday. 4 hrs. $30.

March 3-5—**Sierra Radiology Conference—3rd Annual.** Sacramento Radiology Research and Education Fndn. and No. Calif. Radiological Soc. at North Lake Tahoe. Wednesday-Friday. 18 hrs. $265. Contact: Michael H. Reid, PhD, MD, Sac. Rad. Research and Ed. Fndn., P.O. Box 161112, Sacramento 95816.

March 4-5—**Pathology of Parasitic Infections.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 17 hrs. Contact: Asst. Dir., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 15-18—**International Workshop on Physics and Engineering in Medical Imaging.** UCI at Asilomar Conference Center, Pacific Grove. Monday-Thursday.

March 15-19—**Diagnostic Radiology.** UCSF. Monday-Friday. 33 hrs. $375.

March 24-26—**Gram Negative Organisms: An Approach to Identification.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 20 hrs. Contact: Asst. Dir., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 11-15—**Postgraduate Course in Diagnostic Radiology.** Memorial Hospital Medical Center-UCI Center for Health Education at Disneyland Hotel, Anaheim. Sunday-Thursday. 24 hrs. Contact: Asst. Dir., UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 7-8—**Common Nervous System Pathology Diagnosis and Treatment.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 14 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section. UCSF, Dept. of Rad.,

The Community Cancer Center of

THE HOSPITAL of the GOOD SAMARITAN

presents

Advances in Cancer Detection

THE NINTH ANNUAL SYMPOSIUM

Wednesday

FEBRUARY 17, 1982

THE BILTMORE HOTEL, LOS ANGELES

Faculty

ALISTAIR J. COCHRAN, MD ..... *Los Angeles, CA*
EMERSON DAY, MD ..... *Chicago, IL*
GLORIA FRANKL, MD ..... *Los Angeles, CA*
WILLIAM H. KERN, MD ..... *Los Angeles, CA*
DAN L. LONGO, MD ..... *Bethesda, MD*
C. PAUL MORROW, MD ..... *Los Angeles, CA*
RICHARD H. NALICK, MD ..... *Los Angeles, CA*
WILLIAM M. RICH, MD ..... *Los Angeles, CA*
DONALD G. SKINNER, MD ..... *Los Angeles, CA*

Course Director: JIM S. BONORRIS, MD

FEES: (Luncheon Incl.) $75 MDs; $35 Interns, Residents, Fellows, Retired MDs, Allied Health Professionals

This course is acceptable for up to 7 hours Category I Credit towards CMA and AMA certificates in Continuing Medical Education.

Registration for
ADVANCES IN CANCER DETECTION
Wednesday, February 17, 1982

Name _____ Specialty _____

Address _____ Phone _____

City _____ State _____ Zip _____

Amount Enclosed _____

Please make check payable to: "CANCER SYMPOSIUM"

Mail check and registration form to:

CANCER SYMPOSIUM
The Hospital of the Good Samaritan
616 South Witmer Street
Los Angeles, CA 90017

For More Information:

Bonnie VanWaardenburg
Coordinator of Symposia
(213) 977-2345

Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

January 14-16—**Diagnosis and Treatment of Retinal, Macular and Vitreous Diseases.** Retina Research Fund of St. Mary's Hospital and Medical Center at Canyon Hotel, Palm Springs. Thursday-Saturday. $225. Contact: Howard Schatz, MD, Retina Research Fund of St. Mary's Hosp., 450 Stanyan St., San Francisco 94117. (415) 921-4860.

January 15-16—**Vitrectomy/Ocutome Workshop.** PMC. Friday-Saturday. 12 hrs.

January 16—**Pediatric Urology-Nephrology Seminar.** See Pediatrics, January 16.

January 18-22—**16th Otologic Surgery Course.** House Ear Institute, Los Angeles. Monday-Friday. Contact: Frederick H. Linthicum, Jr., MD, Dir. of Education, House Ear Inst., 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 22-23—**7th Annual Postgraduate Course in Surgery.** UCD at Red Lion Inn, Sacramento. Friday-Saturday.

January 24-28—**Assembly in Surgery.** UCSD at Sheraton Harbor Island, San Diego. Sunday-Thursday.

January 30-February 6—**Office Urology for Urologists.** Univ. of Washington School of Medicine at Hyatt Regency, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 5-7—**National Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery and American Society for Dermatologic Surgery at Century Plaza, Los Angeles. Friday-Sunday. Contact: Drs. Richard Fleming and Toby Mayer, 9730 Wilshire Blvd., Suite 216, Beverly Hills 90212.

February 10-12—**Traumatic and Congenital Hand Surgery.** UCLA. Wednesday-Friday.

February 13-20—**Plastic Surgery.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 18-21—**Pathophysiology and Techniques of Cardiopulmonary Bypass: II.** Cardiothoracic Research and Education Fndn. and Vascular Disease Fndn. at Hilton on Mission Bay, San Diego. Thursday-Sunday. Contact: CREF, P.O. Box 33185, San Diego 92103.

February 26-27—**Ender Nailing: A Motor Skills Course With Hans Ender, MD.** UCD. Friday-Saturday. 11 hrs. $200.

February 28-March 4—**Lake Tahoe Vitreo-Retinal Symposium.** Retinal Faculty, UCD, at Granlibakken Ski Resort, Tahoe City. Sunday-Thursday. Contact: Donald May, MD, 2315 Stockton Blvd., Sacramento 95817. (916) 453-2941.

March 1-5—**Surgical Forum.** Society of Graduate Surgeons at Ambassador Hotel, Los Angeles. Monday-Friday. 31 hrs. $350. Contact: Dir. of Med. Ed., Society of Graduate Surgeons, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 4-5—**13th Annual Lecture and Postgraduate Seminar—Pediatric Ophthalmology and Strabismus Update.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

March 12—**Male Infertility Seminar.** Western Section, American Urological Assn., at Marriott, Los Angeles. Friday. Contact: Kathy De Santis, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

March 18-19—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

March 25-27—**Diagnosis and Treatment of Retinal, Macular and Vitreous Diseases.** Retina Research Fund of St. Mary's Hospital and Medical Center at Silverado Country Club, Napa. Thursday-Saturday. $225. Contact: Howard Schatz, MD, Retina Research Fund of St. Mary's Hosp., 450 Stanyan St., San Francisco 94117. (415) 921-4860.

March 27-31—**19th Annual Seminar on Controversial Areas in Surgery.** UCLA at Palm Springs. Saturday-Wednesday.

March 29-April 2—**Management of Coronary Heart Disease: Medical, Surgical, Exercise.** See Medicine, March 29-April 2.

March 31-April 4—**10th Annual Symposium on Vascular Surgery.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Sunday. $385.

April 2—**Anterior Vitrectomy—1982.** Sutter Community Hospitals at Sutter General Hospital, Sacramento. Friday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

April 15-17—**Postgraduate Course in General Surgery.** UCSF. Thursday-Saturday.

April 17-24—**Frontiers in Functional Neurosurgery.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 21-23—**American Intra-Ocular Implant Society.** Century Plaza, Los Angeles. Wednesday-Friday. Contact: AIOIS, P.O. Box 3140, Santa Monica 90403. (213) 829-7317.

April 23-24—**Vitrectomy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

April 24-May 1—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $325.

April 25-29—**American Association of Neurological Surgeons.** Honolulu. Sunday-Thursday. 40 hrs. Contact: Selene Patterson, AANS, 625 N. Michigan Ave., Suite 1519, Chicago 60611. (312) 944-4205.

May 2-6—**American Society of Colon and Rectal Surgeons—Annual Convention.** San Francisco. Sunday-Thursday. 20 hrs. $125, members: $135, nonmembers. Contact: Harriette Gibson, Admin. Sec., ASCRS, 615 Griswold, Suite 516, Detroit 48226. (313) 961-7880.

May 12—**Surgical Subspecialties.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Secretary, Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

May 14-15—**Diagnostic Ocular and Orbital Ultrasound Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $125. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

OF INTEREST TO ALL PHYSICIANS

January 16—**Herpes Simplex: Clinical Practice and Research.** UCSF Cont. Ed. in Health Sciences at Fort Mason Conference Center, San Francisco. Saturday. $75. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

January 25-29—**Primary Care: Current Management of Common Office Problems.** UCSF. Monday-Friday.

January 28-30—**Modern Drug Therapy.** STAN. Thursday-Saturday. 13 hrs. $250.

January 29-30—**Symposium on Peripheral Vascular Disease.** Harbor-UCLA Medical Center at Disneyland Hotel, Anaheim. Friday-Saturday. 9½ hrs. $135. Contact: Judith Eldridge, Research and Education Inst., B-2 Annex, Harbor-UCLA Med. Ctr., 1124 W. Carson St., Torrance 90502. (213) 533-2847.

February 1-6—**Family Practice Refresher Course.** UCI at Marriott Hotel, Newport Beach. Monday-Saturday.

February 3-5—**Neurology for Non-Neurologists.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

February 6-7—**Immunology for the Family Physician.** UCLA. Saturday-Sunday.

February 6-7—**Hypnosis for Primary Care Physicians: Adjunctive Treatment Modalities for Difficult Medical and Dental Problems.** Alta Bates Hospital, Berkeley. Saturday-Sunday. 14

(Continued on Page 46)

RIMSO®-50
(dimethyl sulfoxide)
50% w/w aqueous solution

INDICATIONS AND USAGE

RIMSO® - 50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. RIMSO ® - 50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.

CONTRAINDICATIONS

None known.

WARNINGS

Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical RIMSO® - 50. The physican should be cognizant of this possibility in prescribing RIMSO® - 50. If anaphylactoid symptoms develop, appropriate therapy should be instituted.

PRECAUTIONS

Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of RIMSO® - 50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation.

Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO® - 50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide.

The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.

DOSAGE AND ADMINISTRATION

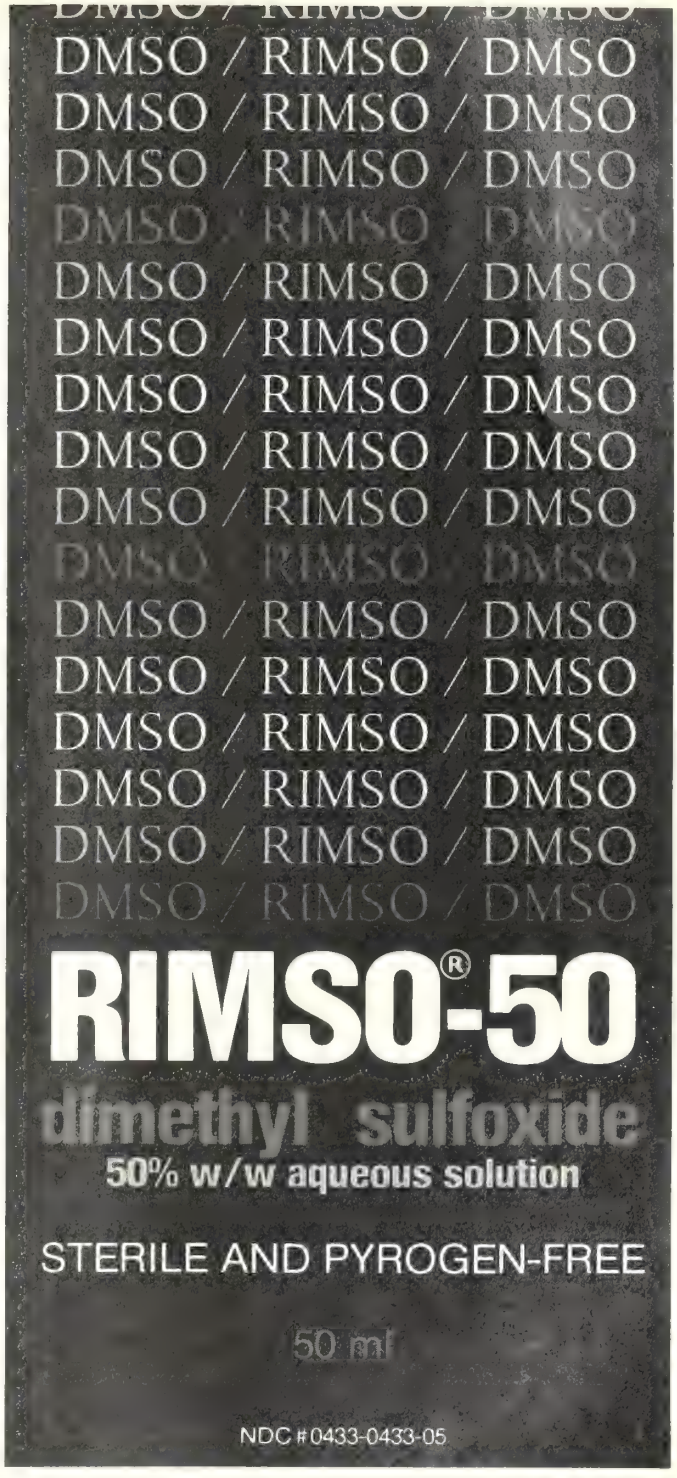
Instillation of 50 ml of RIMSO® - 50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as lidocaine jelly to the uretha is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately.

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO® - 50 can reduce bladder spasm.

In patients with severe interstital cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia. (Saddle block has been suggested).

HOW SUPPLIED

Bottles contain 50 ml of sterile and pyrogen-free RIMSO® - 50 (50% w/w dimethyl sulfoxide aqueous solution).
Dimethyl sulfoxide is clear and colorless.
Protect from strong light.
Store at room temperature (50° to 86°F) (15° to 30°C).
Do not autoclave.
NDC # 0433-0433-05



FOR FURTHER INFORMATION

DRS. NAME

ADDRESS

CITY STATE ZIP

SEND TO: RESEARCH INDUSTRIES CORP.
1847 West 2300 South
Salt Lake City, Utah 84119

Toll-Free (800) 453-8432

(Continued from Page 44)

hrs. Contact: Med. Ed. Dept., Alta Bates Hosp., 3001 Colby St., Berkeley 94705. (415) 845-7110, ext. 2055.

February 7-12—**Winter Sports Injuries.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Friday.

February 10—**Nutrition Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

February 10-12—**32nd Annual Course for Physicians in Family Practice.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. $195. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

February 13-14—**Emotions in Health and Illness.** See Psychiatry, February 13-14.

February 16-19—**Clinical Investigation.** Western Section of Am. Federation for Clinical Research, Western Soc. for Clinical Research, Western Section of Soc. for Investigative Dermatology, Western Soc. for Pediatric Research, and UCSF at Carmel. Tuesday-Friday. 20 hrs. $25, nonmembers + $10 for CME certificate. Contact: Allen D. Cooper, MD, Room S-069, Stanford Med Ctr., Stanford 94305.

February 16-June 8—**Family Practice.** USC. Tuesday evenings. $395.

February 18-19—**Hospital Epidemiology for Physicians and Infection Control Teams.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. Contact: Richard P. Henke, MD, Memorial Hosp., 2801 Atlantic Ave., Long Beach 90801. (213) 595-2431, ext. 23.

February 20-21—**Ninth Annual Family Practice Symposium.** So. Calif. Permanente Medical Group at Marriott, Anaheim. Saturday-Sunday. Contact: Dana Reisman, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-7070.

February 22—**Symposium on Geriatric Medicine.** Sutter Community Hospitals at Red Lion Motor Inn, Sacramento. Monday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

February 22-25—**Critical Care Medicine—20th Annual Symposium.** USC at MGM Grand, Las Vegas. Monday-Thursday. 28 hrs. $295.

February 22-26—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $325.

February 25-28—**8th Annual Basic, Intermediate and Advanced Workshops in Clinical Hypnosis.** UCI and Southern Calif. Society of Clinical Hypnosis at The Grand Hotel, Anaheim. Thursday-Sunday. 28 hrs. Contact: So. Calif. Soc. of Clinical Hypnosis, 4454 Van Nuys Blvd., Suite 215, Sherman Oaks 91403. (213) 872-3350.

March 1-2—**Treatment Issues in Geriatrics.** Western Gerontological Society and Washington State Psychiatric Assn. at Town and Country Hotel, San Diego. Monday-Tuesday. Contact: Barbara Freda, WGS, 785 Market St., Suite 1114, San Francisco 94103. (415) 543-2617.

March 5-6—**Advances in Alcoholism—Third Annual Symposium.** Raleigh Hills Foundation and American Medical Society on Alcoholism at Registry Hotel, Newport Beach. Friday-Saturday. $200. Contact: Kim Hilberg, Raleigh Hills Fndn., 17861 Cartwright Rd., Irvine 92714. (714) 641-1616.

March 5-11—**Annual Postgraduate Convention—Primary Care Update.** LLU School of Medicine Alumni Assn. at LLU. One week. Contact: Beverly Hardt, 11245 Anderson St., Suite 200, Loma Linda 92354. (714) 824-4633.

March 8-12—**Sports Medicine.** Northwestern Univ. Center for Sports Medicine at Maui. Monday-Friday. 25 hrs. Contact: Bates Noble, MD, Northwestern Univ. Ctr. for Sports Medicine, 303 E. Chicago Ave., Chicago 60611.

March 10—**Pain Management.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

March 10-13—**Optimal Health: A Guide for Practicing Physicians.** Scripps Clinic and Research Fndn. at La Costa Resort Hotel, Carlsbad. Wednesday-Saturday. 22 hrs. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

March 12-17—**California Medical Association—111th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Joan Kammerer, CMA.

March 13-20—**Reproductive Endocrinology, Infertility and Contraception.** USC at Maui. One week. $395.

March 15-19—**Sports Medicine.** Ohio State Univ. and Univ. of Hawaii at Princess Kaiulani Hotel, Waikiki, Honolulu. Monday-Friday. 18 hrs. $250. Contact: Joy Lewis, Box CE-CCECS, 2530 Dole St., Honolulu 96822. (808) 948-8244.

March 18-21—**Clinical Management.** STAN at The Lodge, Pebble Beach. Thursday-Sunday. 12 hrs. $175.

March 19—**Diabetes and Nutrition Update.** UC and STAN at Hilton, San Francisco. Friday. Contact: UCD.

March 19-21—**In Pursuit of Wellness.** UCSF at Jack Tar Hotel, San Francisco. Friday-Sunday. $75. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

March 20-24—**American Fertility Society—38th Annual Meeting and 15th Postgraduate Program.** MGM Grand, Las Vegas. Saturday-Wednesday. Contact: Herbert H. Thomas, MD, Med. Dir., AFS, 1608 13th Ave. S., Suite 101, Birmingham, AL 35256. (205) 933-7222.

March 20-27—**Medical Genetics for Health Professionals.** San Jose State University. One week. 15 hrs. Contact: Kate Wright-Rodgers, MPH, Cont. Ed., San Jose State Univ., Washington Square, San Jose 95192. (408) 277-3778.

March 25-27—**Third Annual Dermatology Conference: Dermatology for Non-Dermatologists.** Eisenhower Medical Center and Stanford at Annenberg Center for Health Sciences, Eisenhower Med. Ctr., Rancho Mirage. Thursday-Saturday. Contact: P. Kokemueller, MS, Conf. Services Mgr., Annenberg Ctr. for Health Sciences, Eisenhower Med. Ctr., 39000 Bob Hope Dr., Rancho Mirage 92270.

March 26-27—**Advances in Heart Disease, Aging, Diabetes and Cancer Research.** UCSD at Town and Country Hotel, San Diego. Friday-Saturday. Contact: Robert J. Morin, MD, Harbor-UCLA Med. Ctr., 1000 W. Carson St., Torrance 90509. (213) 533-2233.

March 27-April 3—**Otolaryngology for Non-Otolaryngologists.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 3-10—**Topics in Family Practice.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 10-17—**Management of Pain.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 22-24—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 22-25—**Wound Management.** UCSD at Hilton, San Diego. Thursday-Sunday. 20 hrs.

May 1-8—**Diagnostic and Therapeutic Skills.** USC at Hawaii. One week. 29 hrs. $425.

May 2-5—**Medical Evaluation of the Preoperative Patient.** UCD at Del Monte Hyatt, Monterey. Sunday-Wednesday. 17 hrs. $245.

May 2-5—**American Medical Informatics Association Congress 82—First Annual Joint Conference.** AMIA, Soc. for Advanced Medical Systems, Soc. for Computer Medicine, Internat'l Health Evaluation Assn., Salutis Unitas, Univ. of Missouri-Columbia Health Care Technology Ctr., IL Conf.

on Medical Information Systems, at Hyatt on Union Square, San Francisco. Sunday-Wednesday. Contact: M. F. Collen, MD, 3451 Piedmont Ave., Oakland 94611.

May 3-7—**Symposium on Non-Emergent Outpatient Care.** UCSD at Hilton, San Diego. Monday-Friday. 27 hrs. $325.

May 3-9—**Basic Diving Medicine.** UCSF at Fresno. One week. Contact: Vincent S. O'Hara, MD, VA Medical Center, 2615 E. Clinton, Fresno 93703. (209) 225-6100, ext. 345.

May 12—**Common Fractures.** LLU. Wednesday. 4 hrs. $30.

May 16-21—**Fingers-to-Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Friday. 40 hrs. $375.

May 22-23—**Conference on Health Problems Related to the Chinese in America.** Chinese Hospital and UCSF at Holiday Inn/Financial District, San Francisco. Saturday-Sunday. 12 hrs. $85. Contact: Elizabeth S. Weston, Chinese Hosp., 845 Jackson St., San Francisco 94133. (415) 982-2400, ext. 215.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA

No courses announced.

IDAHO

See Washington Listings, February 13, March 6-13, and June 19-26.

MONTANA

March 20-March 27—**Pulmonary Diseases: A Practical Approach.** Big Sky. Saturday-Saturday. 20 Category I credit hours; also 20 AAFP Elective hours, and 20 ACEP hours. Fee: $260 for Physicians; $180 for Physicians Assistants, Interns and Residents. Contact: M. S. M. Watts, MD, Associate Dean and Director, University of California, San Francisco, Extended Programs in Medical Education, San Francisco, CA 94143. Telephone—For Registration: (415) 666-2894 or 666-2483; for Program Information: (415) 666-4251.

April 15-17—See Washington Listings.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified

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HIDDEN HEALTH HAZARDS IN THE ENVIRONMENT

MARCH 6-7, 1982

Wheeler Auditorium
University of California, Berkeley

Keynote Address

BARRY COMMONER, PhD
Director, Center for the Biology of Natural Systems
Queens College, New York

"Health in the Context of Natural Systems"

Physicians, other health care practitioners, attorneys, researchers, and public administrators will gather to explore the widening gap between environmental health risk research and the working knowledge of health care clinicians.

* * *

SOME SPEAKERS AND TOPICS

RICHARD JACKSON, MD
California Department of Health Services

WARREN WINKLESTEIN, MD
Dean, School of Public Health, UCB

RICHARD WADE
Occupational Safety and Health Administration

RICHARD SPOHN
California Department of Consumer Affairs

DONALD AUSTIN, MD
Chief, Cancer Epidemiology, California Department of Health Services

TED TONG, MD
Bay Area Poison Control Center

PHYLLIS SAIFER, MD
Clinical Ecologist, Berkeley

PHILLIP POLAKOFF, MD
Director, Western Institute of Occupational and Environmental Sciences

Agricultural Exposures, Urban and Rural; Building Environments; Changing Legal and Ethical Considerations; Consumer and Hobby Exposures; Health in the Workplace; Health Psychology of Organizations; Clinical Ecology; Toxic Substance Disposal; Needs for the Future.

* * *

SPONSORS

CENTER FOR PRIMARY CARE STUDIES, UC Irvine School of Medicine
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OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION, STATE OF CALIFORNIA, San Francisco
PHOENIX PROGRAMS, INC., Concord, CA
SCHOOL OF PUBLIC HEALTH, UC Berkeley
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CEU units available for RNs.

For further information, contact:
HEALTH/ENVIRONMENT Conference
P.O. Box 486
Orinda, CA 94563
(415) 655-6847

all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, P.O. Box 9366, Albuquerque, NM 87119 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 247-0539.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 15—**Lythic Therapy Seminar.** Albuquerque. Friday. Savage Auditorium, Presbyterian Hospital Center. 4 credit hours, also AAFP. Contact: Office of Continuing Education, Presbyterian Hospital Center, 1101 Central SE, Albuquerque, NM 87102. (505) 841-1225.

February 5-7—**Advances in Medical Therapeutics II.** Albuquerque. Friday-Sunday. Veterans Administration Medical Center. 18 hours credit, also AAFP Prescribed. Contact: Office of CME, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3942.

February 22-26—**Taos Medical Symposium—Sports Medicine.** Taos. Monday-Friday. Kachina Lodge. 18 credit hours, also AAFP Prescribed. Contact: Dale A. Gray, MD, Taos Medical Symposium, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

February 26-28—**10th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Kachina Lodge. 13 credit hours, also AAFP Prescribed. Contact: American Lung Association of New Mexico, 216 Truman NE, Albuquerque, NM 87108. (505) 265-0732.

March 8-10—**New Mexico Metabolism Seminar.** Taos. Monday-Thursday. Tennis Ranch. 15 credit hours. Contact: Martin J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd. SE, Albuquerque, NM 87108. (505) 842-7000.

March 16-21—**Purgatory Medical Ski Symposium.** Durango, Colorado. Tuesday-Sunday. Iron Horse Resort & Convention Center. 24 credit hours, also AAFP Prescribed. Contact: David R. Holten, MD, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

March 18-19—**Advanced Trauma Life Support Provider's Course.** Albuquerque. Thursday-Friday. UNM Hospital, Burn & Trauma Unit. 16 hours credit. Contact: William Schiller, MD, Director, Burn & Trauma Unit, UNM Hospital, Aubuquerque, NM 87131. (505) 843-2231.

March 30-31—**Base Station Physician Course.** Taos. Tuesday-Wednesday. Sagebrush Inn. 9 credit hours, also AAFP Prescribed. Contact: Arleen L. Sadowsky, MD, President, NM Chapter American College of Emergency Physicians, 6320 Palma Pl. NW, Albuquerque, NM 87120.

April 1-3—**New Mexico Chapter, American College of Emergency Physicians Meeting.** Taos. Thursday-Saturday. Sagebrush Inn. 18 credit hours, also AAFP Prescribed. Contact: Arleen L. Sadowsky, MD, President, 6320 Palma Pl. NW, Albuquerque, NM 87120.

May 5-7—**New Mexico Medical Society Annual Meeting.** Santa Fe. Wednesday-Friday. Hilton Inn. 10 credit hours, also AAFP. Contact: NMMS, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

June 17-19—**Radiology for Family Physicians 1982—An Update.** Santa Fe. Thursday-Saturday. Symposia de Santa Fe. 15 credit hours, also AAFP Prescribed. Contact: Marcus J. Smith, MD PO Box 5175, Santa Fe, NM 87501. (505) 982-5218.

July 8-10—**25th Annual Meeting, New Mexico Ophthalmological Society.** Santa Fe. Thursday-Saturday. Hilton Inn. 8 credit hours. Contact: Walter J. Levy, MD, 465 St. Michael's Dr., Santa Fe, NM 87501. (505) 982-1911.

July 19-22—**25th Annual Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 credit hours. Also AAFP Prescribed. Contact: Convention Director, NM Academy of Family Physicians, PO Box 456, Sunland Park, NM 88063. (505) 247-0539 or (915) 533-3449.

July 23-25—**11th Annual Santa Fe Cardiology Symposium.** Santa Fe. Friday-Sunday. Inn at Loretto. 14 credit hours, also AAFP Prescribed. Contact: Meeting Director, Southwest Cardiology Associates, 8100 Constitution NE, Albuquerque, NM 87110. (505) 292-1114.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

(Continued on Page 50)

DEPARTMENT OF MEDICAL EDUCATION

St. Francis Medical Center

LYNWOOD, CALIFORNIA

presents

3rd Annual T. R. Kidd MD Cardiac Symposium

CARDIOLOGY UPDATE '82: THE BEAT GOES ON

Discussion centering on the revolutionary advances in the diagnosis and treatment of cadiovascular diseases.

FEBRUARY 5-6, 1982

WESTIN BONAVENTURE HOTEL
LOS ANGELES, CALIFORNIA

Distinguished Speakers

ALBERT STARR, MD, FACC, Keynote Speaker
WILLIAM ASHBURN, MD, FACC
RALPH BERG, MD
RICHARD BING, MD, FACC
WILLIAM GANZ, MD, FACC
ROBERT JARVIK, MD
ALBERT KATTUS, MD, FACC
CHARLES KLIEMAN, MD, FACC
JOSEPH K. PERLOFF, MD, FACC
BRAMAH SINGH, MD, D Phil

REGISTRATION FEE: $110

This seminar is accredited for 11 credit hours, Category I Credit

2nd Annual Robert Rabens MD Memorial Symposium

RECENT ADVANCES IN RENAL, METABOLIC & ENDOCRINE DISORDERS

Discussion centering on new and current data as they relate to the pathophysiology and treatment of patients with renal, metabolic and endocrine disorders.

APRIL 16-17, 1982

WESTIN BONAVENTURE HOTEL
LOS ANGELES, CALIFORNIA

Distinguished Speakers

DAVID BERGER, MD
VITO CAMPESE, MD
JACK W. COBURN, MD
ISIDORO COLODRO, MD
WARREN DAVIDSON, MD
STANLEY FRANKLIN, MD
LAWRENCE FROHMAN, MD
RICHARD GLASSOCK, MD
GRANT GWINUP, MD
JOEL KOPPLE, MD
SEYMOUR R. LEVIN, MD
SHAUL G. MASSRY, MD
ROBERT MENDEZ, MD
JOHN NICOLOFF, MD

REGISTRATION FEE: $110

This seminar is accredited for 11 credit hours, Category I Credit

For further information, please contact:

ALLAN M. HOFFMAN, EdD
DIRECTOR OF MEDICAL EDUCATION
ST. FRANCIS MEDICAL CENTER
3630 EAST IMPERIAL HIGHWAY
LYNWOOD, CALIFORNIA 90262
(213) 603-6171

(Continued from Page 48)

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

FAMILY PRACTICE

February 8-12—**Thirteenth Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

MKSAP V REVIEW

(Sponsors: Utah Region, American College of Physicians/Utah Society of International Medicine/University of Utah)
University Medical Center, Salt Lake City

October 1981-June 1982 (Ongoing)—Thursdays. 2 hrs. Fee: $160 (ACP non-members); $60 (ACP members). Contact: John Holbrook, MD (801) 581-7818.

* * * *

January 11-23—**Perinatal/Neonatal Administrative Transport Workshop** (Sponsor: University of Utah). Salt Lake City. Monday-Saturday. Salt Lake Marriott. 58 hrs. Fee: $100-$300. Contact: Jean Thornton, RN (801) 581-7085.

January 13-14—**Diabetes Update** (Sponsor: Regional Medical Education Center/VA Hospital). Salt Lake City. Thursday-Friday. Hotel Utah. 15 hrs. Fee: $50. Contact: Nancy Harrison (801) 582-1565, ext. 1100.

January 16-20—**Immune Consequences of Thermal and Traumatic Injury** (Sponsor: University of Utah). Snowbird. Saturday-Wednesday. 18 hrs. Fee: $245. Contact: Claire Turner (801) 581-7617.

January 22—**Anterior and Posterior Segment Photocoagulation** (Sponsor: University of Utah). Salt Lake City. Friday. Research Lecture Hall, UUMC. 6 hrs. Fee: $50. Contact: Mano Swartz, MD (801) 581-6384.

January 29-30—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

February 8-11—**11th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Salt Lake City. Monday-Thursday. Salt Lake Hilton. 32 hrs. Fee: $250. Contact: Linda Twitchell (801) 581-8633.

February 12-16—**27th Annual Postgraduate Course in Anesthesiology: Anesthesiology and the Lung** (Sponsor: University of Utah). Salt Lake City. Friday-Tuesday. Hotel Utah. 17 hrs. Fee: $250. Contact: T. Stanley, MD (801) 581-6393.

February 15-19—**Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Park City. Monday-day-Friday. Holiday Inn. 25 hrs. Fee: $300. Contact: John Matsen, MD (801) 581-5514.

February 20-23—**23rd Annual OB/GYN Course** (Sponsor: University of Utah). Park City. Saturday-Tuesday. The Yarrow. 14 hrs. Fee: $275. Contact: David Engleberg (801) 581-3087.

February 20-27—**The Snowbird Conference on Modern Diagnostic Methods in Internal Medicine** (Sponsors: George Washington University Medical Center, Washington, DC/ Academy of Continuing Medical Education, Salt Lake City). Snowbird. Saturday-Saturday. 15 hrs. Fee: $245 (Residents: $150). Contact: Gregg P. Thomas, CME Office, George Washington University Medical Center, 2300 Eye Street, NW, Washington, DC 20037. (202) 676-4285.

February 24-26—**Training and Certification for Pulmonary Function Testing (Spirometry)** (Sponsors: University of Utah/ Rocky Mountain Center for Occupational and Environmental Health). Park City. Wednesday-Friday. The Yarrow. 18 hours. Fee: $350. Contact: Ms. K. Blosch (801) 581-5710.

February 24-27—**Reproductive Endocrinology and Infertility Update** (Sponsor: University of Utah). Park City. Wednesday-Saturday. The Yarrow. 14.5 hrs. Fee: $275. Contact: David Engleberg (801) 581-3087.

March 1-3—**Common Problems in Pediatrics—Intermountain**

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

Pediatric Society Annual Scientific Meeting (Sponsor: University of Utah). Salt Lake City. Monday-Wednesday. Little America. 15 hrs. Fee: $190. Contact: Jacque Bachtell (801) 581-3729.

March 1-5—**7th Annual Advances in Internal Medicine** (Sponsor: University of Utah). Snowbird. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 6-13—**4th Annual Park City Radiology Conference** (Sponsor: University of Utah). Park City. Saturday-Saturday. Holiday Inn. 20 hrs. Fee: $290. Contact: P. Ruben Koehler, MD (801) 581-8188.

March 8-12—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Snowbird. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 13-20—**First Annual Oculo-Plastic SRI Meeting** (Sponsor: University of Utah). Park City. Saturday-Saturday. 15 hrs. Fee: $225. Contact: Darrel Wolfley, MD (801) 363-3355.

March 15-19—**Second Annual Nutrition in Contemporary Medicine Course** (Sponsor: University of Utah). Park City. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 18-19—**Infection Control Update—Rocky Mountain Infection Control Association (RMICA)** (Sponsor: University of Utah). Salt Lake City. Thursday-Friday. Little America. 12 hrs. Fee: $75. Contact: Sego Matsumiya (801) 582-1565.

March 20-27—**Park City Dermatological Seminar** (Sponsor: Intermountain Dermatology Foundation [IDF]). Park City. Saturday-Saturday. Shadow Ridge Condo Hotel. 16 hrs. Fee: $250. Contact: IDF, 1151 East 3900 South, Salt Lake City 84117 (801) 268-0435.

March 24-25—**Genetics: Impact of Genetic Disorders on the Family** (Sponsor: University of Utah). Salt Lake City. Wednesday-Thursday. University of Utah Medical Center. 12 hrs. Fee: $50-$65. Contact: John Carey, MD, (801) 581-8943.

March 26-27—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

April 7-9—**Health Hazards of Minerals and Mining: 4th Annual Park City Environmental Health Conference** (Sponsors: University of Utah/Rocky Mountain Center for Occupational and Environmental Health). Park City. Monday-Wednesday. 24 hrs. Fee: $300. Contact: Katharine Blosch (801) 581-5710.

April 15-17—**First Annual Clinical Ophthalmology Meeting at Snowbird** (Sponsor: University of Utah). Snowbird. Tuesday-Thursday. 9 hrs. Fee: $50. Contact: Rebecca Olsen (801) 581-6384.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

January 14-15—**Sexual Disorders in Medical Practice.** Seattle. Thursday-Friday. Seattle Hilton. Contact: U/W.

January 15—**Perspectives in Rheumatology and Clinical Immunology.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

January 19—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

January 20—**Sodium, Potassium & Hypertension.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

CompuMed Systems now offers the private practitioner in-office computer-assisted ECG analysis...with no capital investment in equipment. Complete 3 channel, 10 wire, 12 lead ECG connects directly from your patient to our powerful, hospital-proven computer via phone terminal. You receive hard copy print-out analysis in three minutes. Overread available from board certified cardiologist.

CompuMed is a pay-for-use service, with no equipment to buy and no capital investment.

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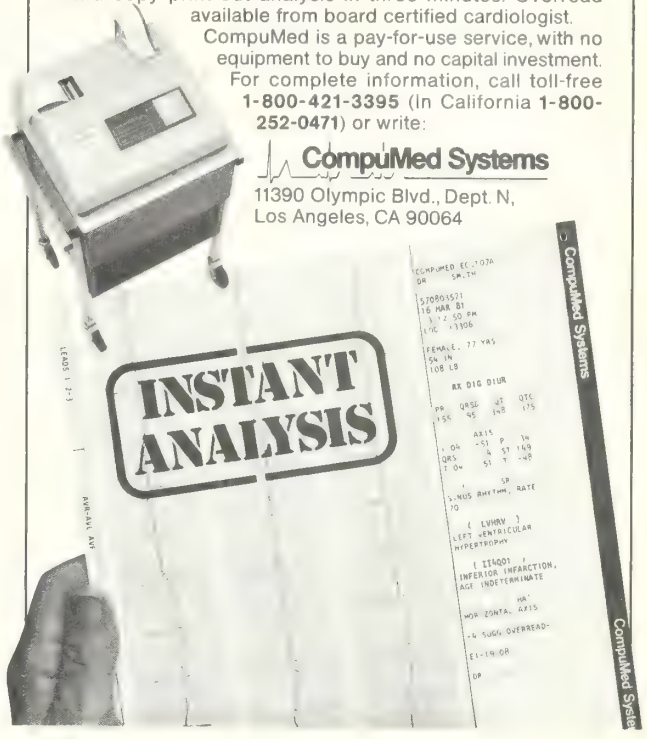
CompuMed Systems
11390 Olympic Blvd., Dept. N,
Los Angeles, CA 90064



SYMPOSIUM MAUI, INC.
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Presents

ALLERGY FOR THE FAMILY PRACTITIONERS

with Selected Topics on Hawaiian Family Culture and Medical Practices

MARCH 8-13, 1982

Royal Lahaina Resort, Kaanapali Beach, Maui

This is a program designed for the Family and General Practitioner to discuss the office treatment of allergic disorders. It is a practical and scientific course that demonstrates how both the standard allergist and the Rinkel allergist test and treat patients.

OPTIONAL ONE-DAY TOUR

Kalaupapa, Moloka'i—Immunology of Leprosy

This program has been reviewed and is acceptable for 24 prescribed hours by the American Academy of Family Practitioners.

For information and registration contact:

JOE HARRISON, MD, Program Director
SYMPOSIUM MAUI, Inc.
Box 10185
Lahaina, Maui, Hawaii 96761

January 21-22—**Beta Block/Calcium Antagonists.** Seattle. Thursday-Friday. Seattle Hilton. Contact: U/W.

January 21-23—**Retina and Vitreous.** Seattle. Thursday-Saturday. Doubletree Plaza Hotel. Contact: Marcia Wahlman, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 25—**Legionnaires/New Pneumonias/Toxic Shock.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

January 27—**(MONTANA) Nosocomial/Urinary Infections.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

January 27—**(ALASKA) Genital Herpes/Simplex Infection.** Anchorage. Wednesday. Contact: U/W.

January 28—**(MONTANA) Nosocomial/Urinary Infections.** Billings. Thursday. Marillac Hall. Contact: U/W.

January 28-29—**Financial Planning for Physicians.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

January 28-30—**(OREGON) Cytology Continuing Education Workshop.** Portland. Thursday-Saturday. Contact: CME Harborview.

January 29—**(MONTANA) Nosocomial/Urinary Infections.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

January 30-February 6—**(HAWAII) Office Urology for Urologists.** Maui. Saturday-Saturday. Hyatt Regency. Contact: U/W.

January 31-February 7—**(MEXICO) Surgical Management of Trauma.** Puerto Vallarta. Sunday-Sunday. Camino Real. Contact: U/W.

February 1—**Fifth Annual Cancer Conference.** Everett. Monday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

February 1—**Site Visit.** Omak. Monday. Contact: U/W.

February 1—**(ALASKA) Site Visit.** Ketchikan. Monday. Contact: U/W.

February 3—**(ALASKA) Hysterical Psychosis.** Anchorage. Wednesday. Contact: U/W.

February 3—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

February 4—**(IDAHO) Site Visit.** Pocatello. Thursday. Contact: U/W.

February 5-6—**Case Studies in Internal Medicine.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 6-13—**(IDAHO) Office Orthopaedics.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

February 8—**(MONTANA) Site Visit.** Kalispell. Monday. Contact: U/W.

February 9—**(MONTANA) Site Visit.** Whitefish. Tuesday. Contact: U/W.

February 12—**Nutrition in Hospitalized Patients.** Seattle. Friday. Park Hilton. Contact: U/W.

February 13-20—**(HAWAII) Plastic Surgery.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

February 13-20—**(IDAHO) Infectious Diseases.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

February 17—**Advances in Diabetes.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

February 17—**(MONTANA) Laboratory/Clinical Management Rheumatologic Disorders.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

February 18—**(MONTANA) Laboratory/Clinical Management Rheumatologic Disorders.** Billings. Thursday. Marillac Hall. Contact: U/W.

February 18-19—**Sports Medicine in the Emergency Room.** Wenatchee. Thursday-Friday. Thunderbird Motor Inn. Contact: Heidi Hilby, Washington Chapter, American College of Emergency Physicians, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

February 19—**(MONTANA) Laboratory/Clinical Management Rheumatologic Disorders.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

February 20-27—**(HAWAII) Cardiology.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

February 22—**Mt. St. Helens: Health Effects—Lung.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

February 24-26—**American College of Physicians: Clinical Topics in Pulmonary Disease.** Seattle. Wednesday-Friday. Virginia Mason Medical Center. Contact: VMMC.

February 26-27—**Stroke: Current Concepts.** Seattle. Thursday-Friday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education and Training Department, 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

February 26-28—**Cytology Continuing Education Workshop.** Seattle. Friday-Saturday. Northwest Hospital. Contact: CME Harborview.

February 27—**Behavioral Techniques in Primary Care.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Ed Oshiro, Office of Medical Education, Group Health Cooperative of Puget Sound, 200 15th Avenue East, Seattle, WA 98112. (206) 326-7348.

March 1-2—**(CALIFORNIA) Washington State Psychiatric Association: Treatment Issues in Geriatrics.** San Diego. Monday-Tuesday. Town and Country Hotel. Contact: Barbara Freda, Western Gerontological Society, 785 Market Street, Suite 1114, San Francisco, CA 94103. (415) 543-2617.

March 1-2—**Computers in Continuing Education.** Seattle. Monday-Tuesday. U/W Health Sciences Building. Contact: U/W.

March 4-5—**Gynecology for Primary MDs.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 5—**Adolescent Medicine.** Seattle. Friday. Children's Orthopedic Hospital and Medical Center. Contact: U/W.

March 6—**Handicapped Child.** Seattle. Saturday. Children's Orthopedic Hospital and Medical Center. Contact: U/W.

March 6-13—**(IDAHO)—Perinatal Critical Care.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

March 11-12—**Tacoma Academy of Internal Medicine—Annual Meeting.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 15—**(IDAHO) Site Visit.** Boise. Monday. Contact: U/W.

March 16—**Prevention/Treatment Thromboembolism.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

March 16—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

March 17—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

March 17—**Vasculitis.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

March 18—**(ALASKA) Stress Management With Children.** Anchorage. Thursday. Contact: U/W.

March 18-19—**Depression and Anxiety.** Seattle. Thursday-Friday. U/W Health Sciences Bldg. Contact: U/W.

March 19—**Common Psychiatry Problems for Primary Care.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

March 19-20—**Days of Pediatrics.** Tacoma. Friday-Saturday. Contact: CME Pierce County.

March 22—**Diagnosis and Management of Vasculitis.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

March 24—**(MONTANA) Recent Advances in Hematology.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

March 24—**(ALASKA) Cancer & Pregnancy.** Anchorage. Wednesday. Contact: U/W.

March 25—**(MONTANA) Recent Advances in Hematology.** Billings. Marillac Hall. Contact: U/W.

March 26—**(MONTANA) Recent Advances in Hematology.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

March 26-27—**Recombinant DNA for the Clinician.** Seattle. Friday-Saturday. U/W Health Science Bldg. Contact: U/W.

March 27-April 3—**(HAWAII) Obstetrics and Gynecology.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 27-April 3—**(HAWAII) Otolaryngology for Non-Otolaryngologists.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

March 29-April 9—**Rehabilitation Medicine Review.** Bellevue. Monday-Friday. Bellevue Hilton. Contact: U/W.

March 31—**Medicine and Civilization.** Seattle. Wednesday. U/W Health Sciences Building. Contact: U/W.

April 3-10—**(HAWAII) Topics in Family Practice.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 7, 14, 21, 28, May 5—**Medicine and Civilization.** Seattle. Wednesdays. U/W Health Sciences Building. Contact: U/W.

April 8—**Dermatology Conference.** Everett. Thursday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

April 9-10—**Management of Obesity: Scientific Approach.** Seattle. Friday-Saturday. Park Hilton. Contact: U/W.

April 10—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

April 10-17—**(HAWAII) Management of Pain.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 15-17—**(MONTANA) Cytology Continuing Education Workshop.** Billings. Thursday-Saturday. Contact: CME Harborview.

April 17-24—**(HAWAII) Frontiers in Functional Neurosurgery.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 19—**(IDAHO) Early Cervical Cancer.** Boise. Monday. Contact: U/W.

April 20—**Detection/Rx Early Cervical Cancer.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

April 21—**(MONTANA) What's New in Diabetes.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

April 21—**Interstitial Lung Dis/Pulmonary Nodules.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

April 22—**(MONTANA) What's New in Diabetes.** Billings. Thursday. Marillac Hall. Contact: U/W.

April 22-23—**Vascular Diseases.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

April 23—**(MONTANA) What's New in Diabetes.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

April 26—**Urinary Infections New Developments in Nosocomial Infections.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

April 28—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

April 28-30—**Children's Orthopedic Hospital and Medical Center 75th Anniversary Pediatric Symposium.** Seattle. Wednesday-Friday. Children's Orthopedic Hospital and Medical Center. Contact: Donna Neumann, Medical Administration Office, Children's Orthopedic Hospital and Medical Center, P.O. Box 65371, Seattle, WA 98105. (206) 634-5377.

April 29—**Trauma.** Seattle. Thursday. Museum of History and Industry. Contact: U/W.

May 3—**Site Visit.** Omak. Monday. Contact: U/W.

May 3—**(ALASKA) Site Visit.** Ketchikan. Monday. Contact: U/W.

May 4—**(ALASKA) Site Visit.** Anchorage. Tuesday. Contact: U/W.

May 4—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

May 6-7—**(ALASKA) Cross Cultural Child Psychiatry.** Anchorage. Thursday-Friday. Contact: U/W.

May 7—**The Foot.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

May 13-15—**Third Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 14—**Medical Alumni.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

May 14-15—**Therapeutics in Common Medical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 19—**Breast Cancer & Acute Leukemia.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

May 20—**Estrogen Controversy.** Tacoma. Thursday. Contact: CME Pierce County.

May 21-22—**Topics in Emergency Room Medicine: The First 60 Minutes.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

May 24—**Fever Unknown Origin/Dx Elderly Dementia.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

May 26—**(ALASKA) Vaginitis.** Anchorage. Wednesday. Contact: U/W.

May 26—**(MONTANA) Health Problems of Physicians.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

May 26—**(MONTANA) Site Visit.** Kalispell. Wednesday. Contact: U/W.

May 27—**(MONTANA) Health Problems of Physicians.** Billings. Thursday. Marillac Hall. Contact: U/W.

May 27—**(MONTANA) Site Visit.** Whitefish. Thursday. Contact: U/W.

May 27-28—**Current Concepts in Management of Joint Disease.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

May 28—**(MONTANA) Health Problems of Physicians.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

May 29—**(IDAHO) Site Visit.** Pocatello. Saturday. Contact: U/W.

June 7—**(MONTANA) Site Visit.** Kalispell. Monday. Contact: U/W.

June 7—**(ALASKA) Site Visit.** Ketchikan. Monday. Contact: U/W.

June 8—**(ALASKA) Site Visit.** Anchorage. Tuesday. Contact: U/W.

June 8—**(MONTANA) Site Visit.** Whitefish. Tuesday. Contact: U/W.

June 11-12—**Common Minor Surgeries.** Seattle. Friday-Saturday. Park Hilton. Contact: U/W.

June 14—**(IDAHO) Vaginitis.** Boise. Monday. Contact: U/W.

June 14—**Site Visit.** Omak. Monday. Contact: U/W.

June 14-18—**Advances in Family Practice.** Seattle. Monday-Friday. Seattle Hilton. Contact: U/W.

June 15—**Vaginitis.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

June 15—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

June 16—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

June 17-18—**(ALASKA) Behavior Medicine for GP's.** Anchorage. Thursday-Friday. Contact: U/W.

June 19-23—**(BRITISH COLUMBIA, CANADA) Canadian Congress of Laboratory Medicine & Pacific Northwest Society**

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: June 6-8, 1982, Chena Hot Springs.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. House of Delegates' Annual Meeting: May 28-29, 1982, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 12-17, 1982, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 21-24, 1982, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: 1982—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 28-31, 1982, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: 1982—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 14-16, 1982, MGM Grand Hotel, Reno.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 5-7, 1982, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: 1982—date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: 1982—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 7-10, 1982, Towne Motel, Yakima.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82001. Midwinter Seminar January 7-9, 1982, Teton Village, Jackson. Annual Meeting: June 30-July 3, 1982, Jackson Lake Lodge, Moran.

of Pathologists Meeting. Vancouver, BC. Saturday-Wednesday. Hotel Vancouver. Contact: G. R. Gray, MD, 201-660 West Seventh Avenue, Vancouver, BC V5Z IB5.

June 19-26—**(IDAHO) Radiology Northwest V.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

June 21-25—**Internal Medicine Review.** Seattle. Monday-Friday. Park Hilton. Contact: U/W.

June 23-27—**(OREGON) Ethics and History with Shakespeare.** Ashland. Wednesday-Sunday. Ashland Inn. Contact: U/W.

June 24-25—**EKG Interpretation and Arrythmias.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

June 24-26—**Medical Aspects of Dance.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact: U/W.

June 28—**Recent Advances in Hematology.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

July 23-25—**Washington State Society of Anesthesiologists: Seafair IV Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center. Contact: VMMC.

August 19-21—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

September 8-15—**13th International Cancer Congress.** Seattle. Wednesday-Wednesday. Seattle Center. Contact: Congress Operations Office, 13th International Cancer Congress, Fourth and Blanchard Building, Suite 1800, Seattle, WA 98121. (206) 621-9440.

September 16-18—**(WYOMING) Cytology Continuing Education Workshop.** Jackson. Thursday-Saturday. Contact: CME Harborview.

September 23-25—**Cytology Continuing Education Workshop.** Renton. Thursday-Saturday. Valley General Hospital. Contact: CME Harborview.

WYOMING

January 7-9—**Wyoming Medical Society Midwinter Seminar.** Jackson. Thursday-Saturday. Teton Village. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne, WY 82001. (307) 635-2424.

June 30-July 3—**Wyoming Medical Society Annual Meeting.** Moran. Wednesday-Saturday. Jackson Lake Lodge. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne. WY 82001. (307) 635-2424.

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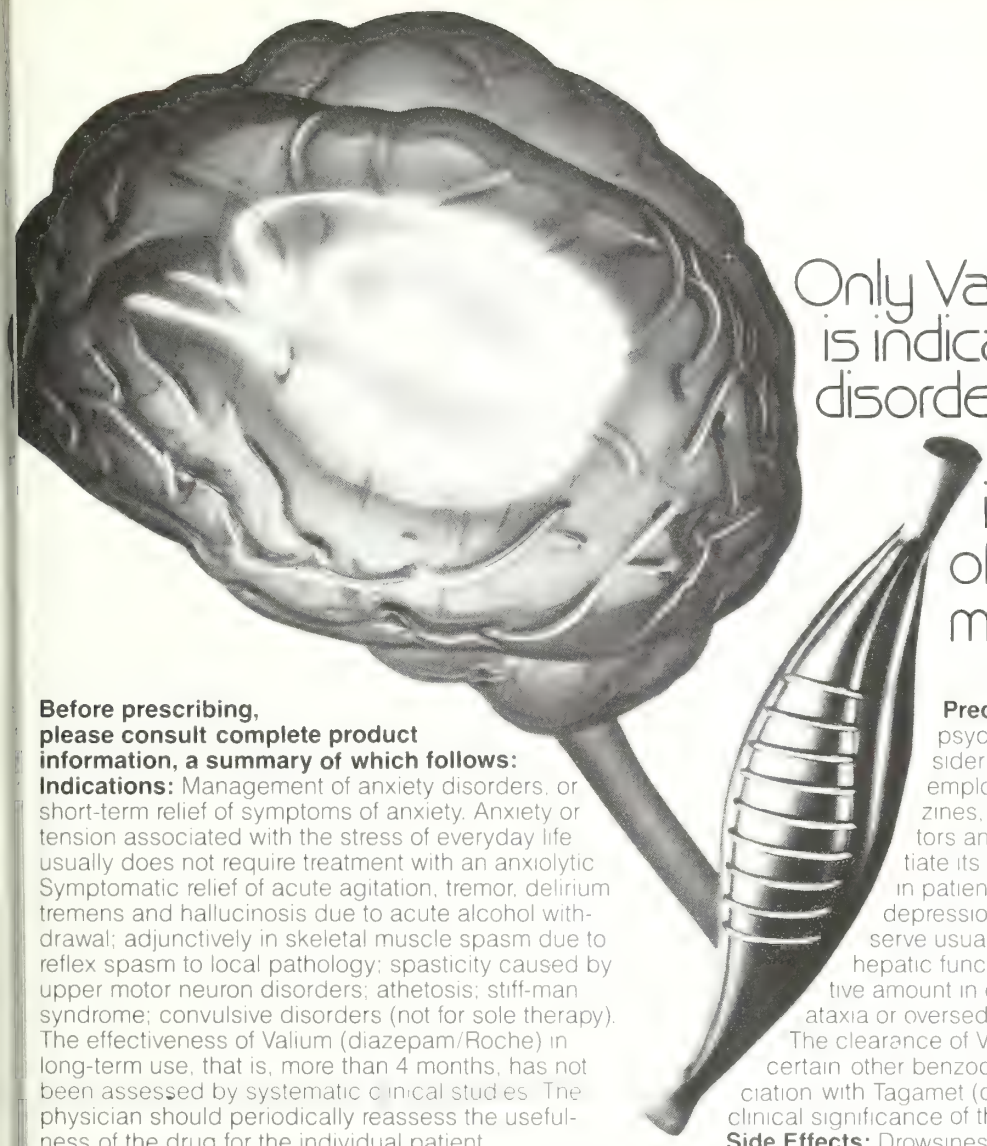


Only Valium® (diazepam/Roche) is indicated in anxiety disorders and as an adjunct in the relief of skeletal muscle spasm

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy). The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium (diazepam/Roche) and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

How Supplied: For oral administration, Valium scored tablets—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100* and 500;* Prescription Paks of 50, available in trays of 10.* Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25,† and in boxes containing 10 strips of 10.†

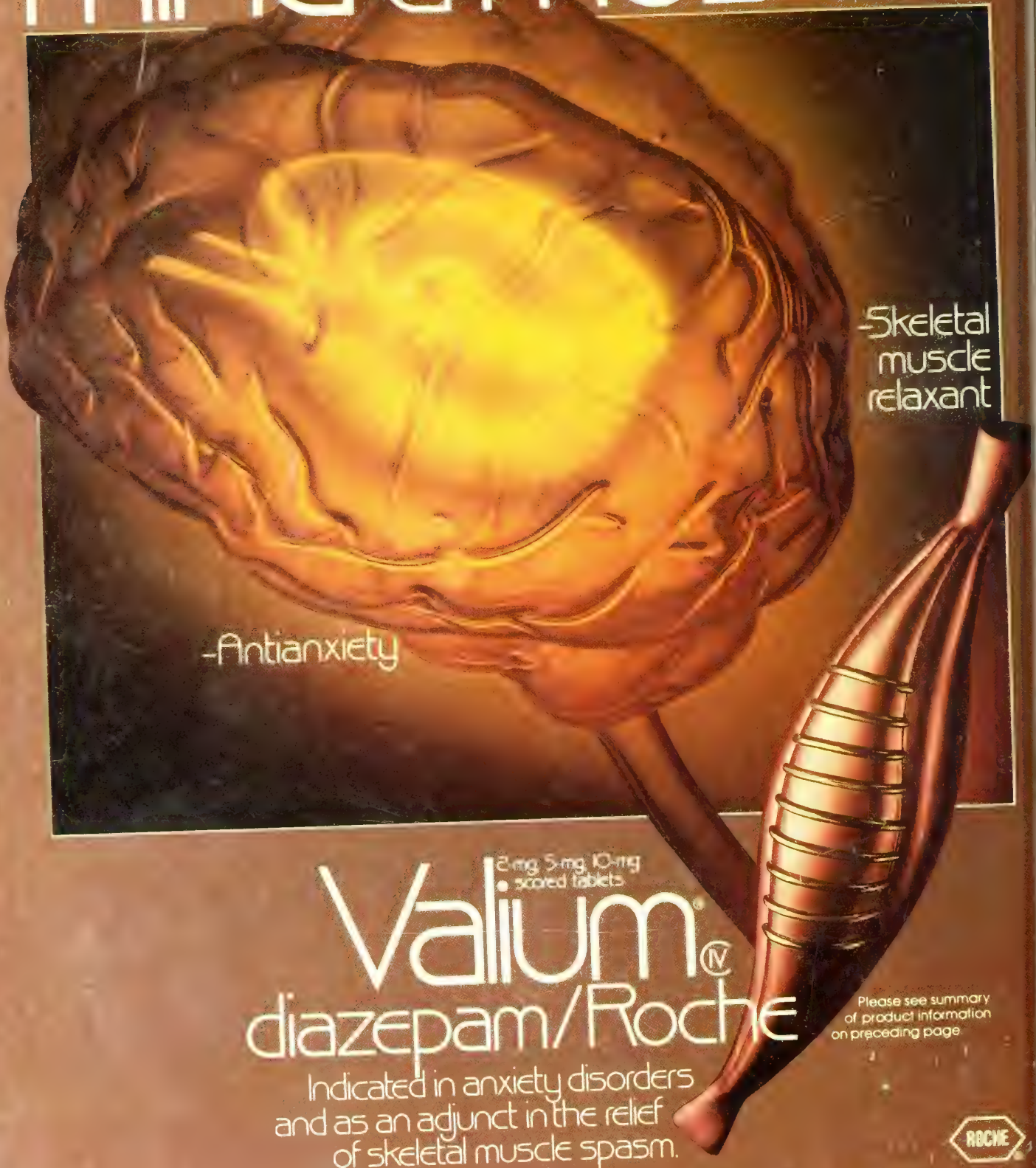
*Supplied by Roche Products Inc., Manati, Puerto Rico 00701
†Supplied by Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, New Jersey 07110

ROCHE

ROCHE PRODUCTS INC
Manati, Puerto Rico 00701

Only Valium® (diazepam/Roche)
has these two distinct effects

mind & muscle



2-mg, 5-mg, 10-mg scored tablets

Valium® (IV)
diazepam/Roche

Please see summary of product information on preceding page

Indicated in anxiety disorders and as an adjunct in the relief of skeletal muscle spasm.

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THE WESTERN Journal of Medicine

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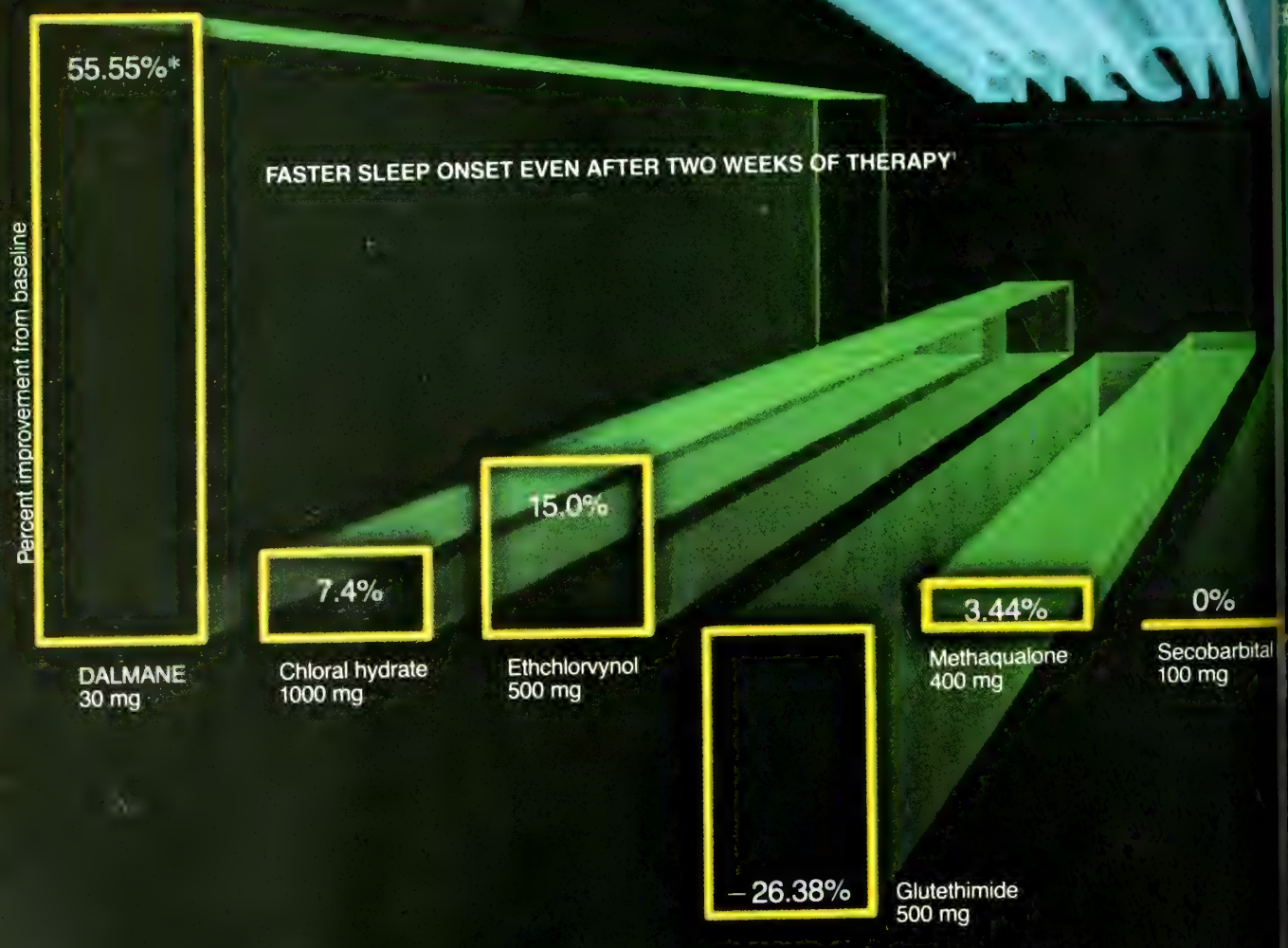
★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA; IDAHO; MONTANA; NEW MEXICO; OREGON; UTAH; WASHINGTON; W**
(See Advertising Page 21)

★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association**

EFFECTIVE



THE MOST INTENSIVELY STUDIED SLEEP MEDICATION

Efficacy of Dalmane (flurazepam HCl/Roche) has been documented in 9141 insomniac patients evaluated in 185 clinical studies. In addition, Dalmane efficacy has been proven in the sleep research laboratory during 995 subject nights.[2]

WITH AN UNSURPASSED RECORD OF SAFETY

In a study of 2542 hospitalized medical patients with insomnia, adverse reactions were reported in only 3.1% or 78 patients. These reactions consisted predominantly of unwanted residual drowsiness; none were considered serious by attending physicians.[3] Safety has also been demonstrated by lack of interference with many commonly ordered laboratory tests [4,5] and no unacceptable fluctuation in prothrombin time in patients on chronic warfarin therapy.[6,7]

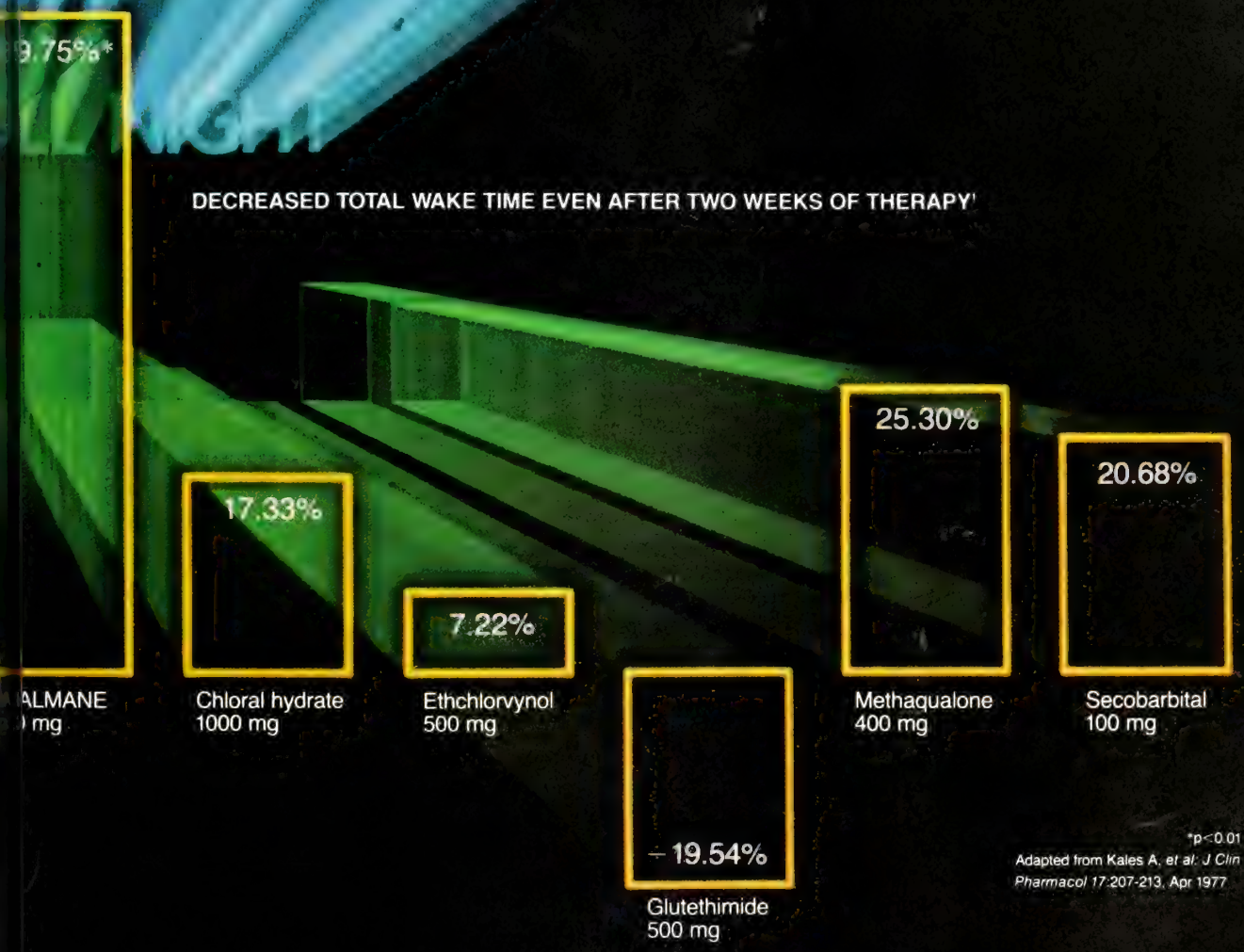
AND SLEEP WITHIN 17 MIN NO WORSENING OF SLEEP ON DISCONTINUAT

Rapid sleep induction, within 17 minutes on average,[3] sets the s for insomnia relief, with improve ment that continues.

In reviewing the experience a discontinuation of Dalmane (flurazepam HCl/Roche) for pe ranging up to 14 nights, no wor ing of sleep compared with bas was observed.[8]

Should insomnia recur, the p may require guidance in setting regular sleep program to help p

ALL NIGHT



DECREASED TOTAL WAKE TIME EVEN AFTER TWO WEEKS OF THERAPY[1]

*$p<0.01$

Adapted from Kales A, *et al*: *J Clin Pharmacol* 17:207-213, Apr 1977

he optimum environment for
nset of natural sleep. If hypnot-
rapy is required, it should be
for the shortest time at the
t effective dose to achieve the
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ients receiving Dalmane
zepam HCl/Roche) should be
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g in hazardous occupations
ing complete mental alertness
as operating machinery or
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Please see following page for a summary of product information.

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One 15-mg capsule *h.s.*–recommended initial dosage for elderly or debilitated patients.
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(15 mg may suffice in some patients)

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–which can cause transient insomnia in the elderly[10]

–which can require careful monitoring in cardiovascular patients[10]

–which have strong anticholinergic effects[10]

Antihistamines

–which are *not* reliable sleep-inducing agents[11]

–which may produce stimulation instead[11]

–which have anticholinergic effects[11]

Major tranquilizers

–whose side effects may be troublesome for nonpsychotic patients[12]

–where tolerance for sedation appears rapidly[12]

Dalmane does not cause significant worsening of sleep beyond baseline levels upon discontinuation.[8]

References: **1.** Kales A, *et al*: *J Clin Pharmacol* 17:207-213, Apr 1977 **2.** Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **3.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther* 21:355-361, Mar 1977 **4.** Moore JD, Weissman L: *J Clin Pharmacol* 16:241-244, May-Jun 1976 **5.** Spiegel HE: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **6.** Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, pp. 641-646 **7.** Warfarin Study Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **8.** Kales A, *et al*: *Clin Pharmacol Ther* 18:356-363, Sep 1975 **9.** Baldessarini RJ: Drugs and the treatment of psychiatric disorders, chap. 19, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co. Inc., 1980, pp. 391-447 **10.** Cole JO, Davis JM: Antidepressant drugs, chap. 31.2, in *Comprehensive Textbook of Psychiatry II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2. Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp. 1941-1956 **11.** Douglas WW: Histamine and 5-hydroxytryptamine (serotonin) and their antagonists, chap. 26, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co Inc., 1980, pp. 609-646 **12.** Davis JM, Cole JO: Antipsychotic drugs, chap. 31.1, in *Comprehensive Textbook of Psychiatry/II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2. Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp. 1921-1940

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.

Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

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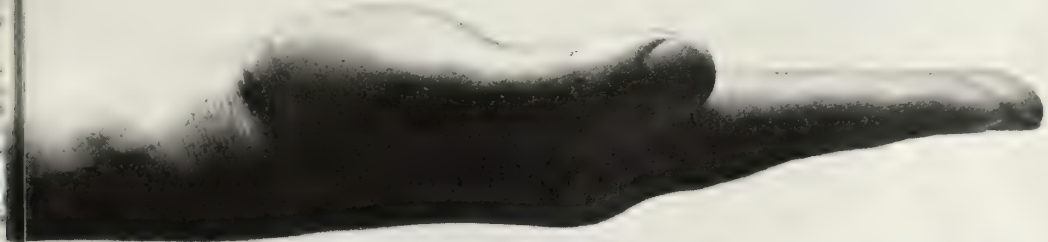

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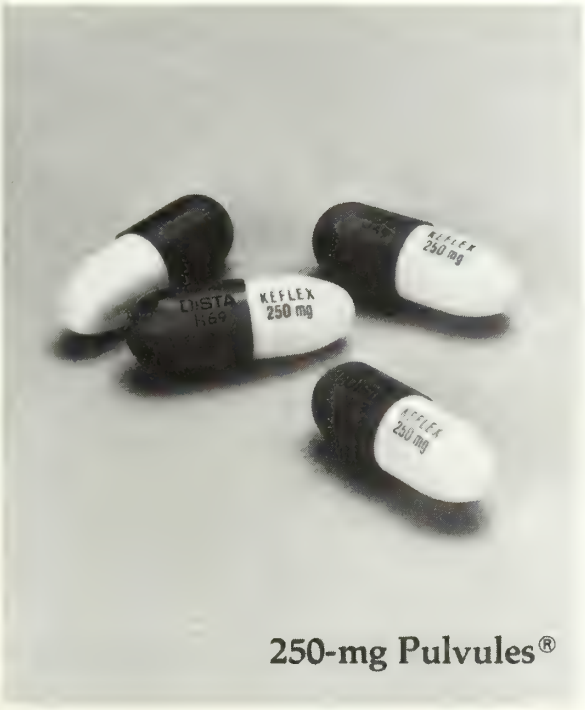

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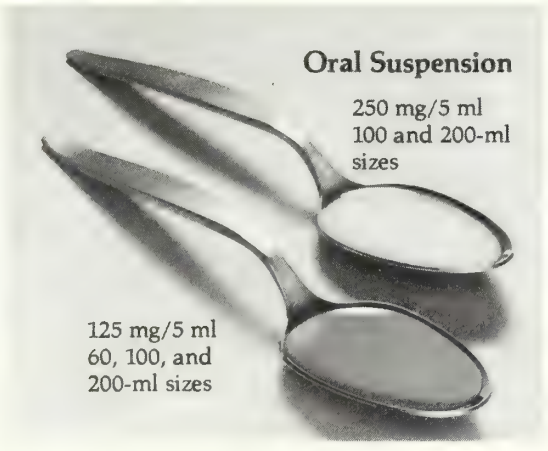

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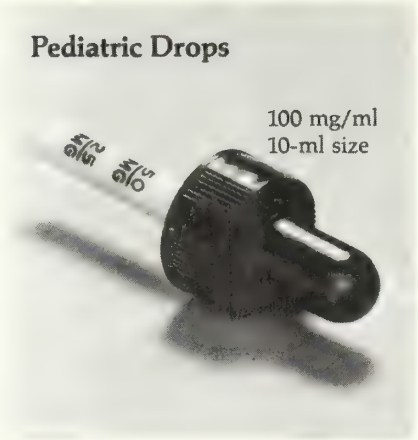

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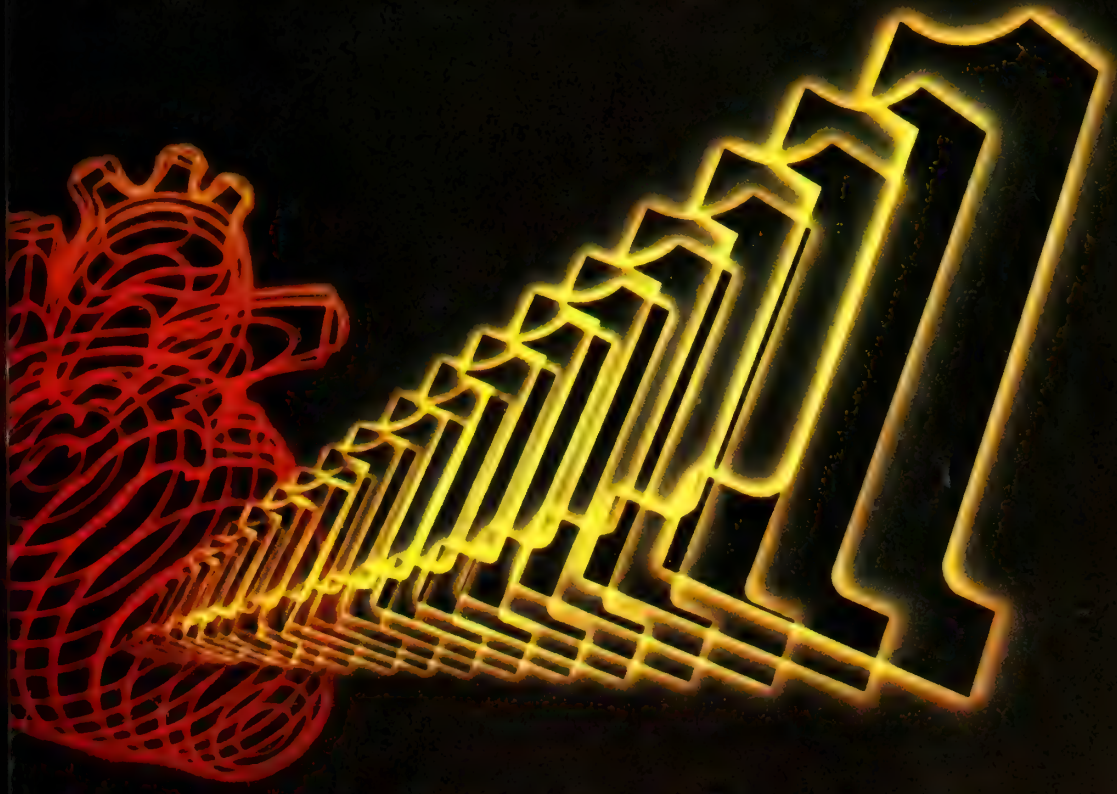

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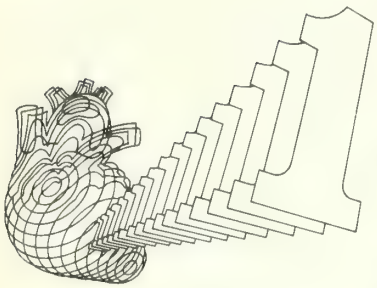

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Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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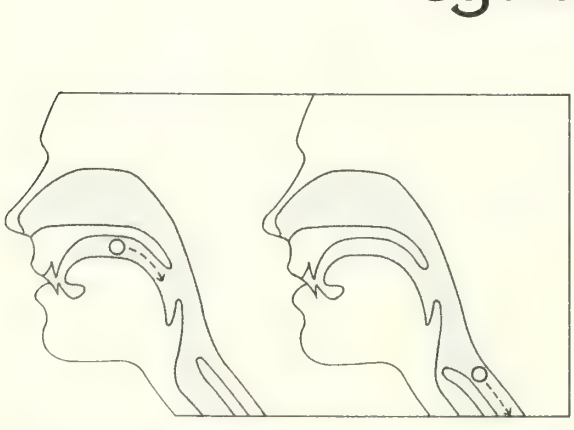
Better tolerated than regular aspirin



Now, by means of a unique water-soluble cellulose coating, Improved Bayer® Aspirin provides oro-pharyngo-esophageal protection for your patients. Furthermore, in a recent short term use study, perceived stomach upset was shown to be no greater than seen with placebo.[1]

This patented coating is *not* enteric in nature, so it is not affected by pH. And the film does not affect absorption or bioavailability. What it does is to stay intact just long enough for tablets to reach the stomach. Disintegration in the buccal cavity, pharynx and esophagus is avoided—easing swallowing and minimizing aspirin

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Protective effect demonstrated in multi-center study[1]

In a double-blind, multi-center clinical study,[1] involving 907 subjects, Improved Bayer Aspirin was shown significantly superior to regular aspirin in avoiding aspirin taste, aftertaste, dissolution of tablets in the mouth and burning in the throat.

As well tolerated as placebo

What's more, for short term use when compared to both coated and uncoated placebo tablets, Improved Bayer Aspirin showed *no significant difference in subjective complaints of stomach upset*-as shown in the chart:

Subjective evaluations—average percentage of complaints following each of three 650 mg doses of Improved Bayer Aspirin, placebo and coated placebo—given four hours apart[1]

Symptom & Time of Administration*	Improved Bayer Aspirin	Placebo	Coated Placebo
Burning in Throat			
5 min.	6%	5%	5%
20 min.	8%	7%	8%
50 min.	6%	5%	5%
Stomach Upset			
5 min.	2%	4%	2%
20 min.	6%	8%	5%
50 min.	8%	7%	5%
Nausea			
5 min.	0%	1%	0%
20 min.	2%	3%	2%
50 min.	3%	2%	2%

* Following each of the three doses of test formulations, subjective side effects were recorded at 5, 20 and 50 minutes.

Better patient compliance

With its low incidence of subjective complaints and high degree of acceptance, Improved Bayer Aspirin can help assure the kind of patient compliance needed for successful salicylate therapy.

Now, more than ever—Bayer is the name to specify

To be sure your patients get all the benefits of Improved Bayer Aspirin, be sure to specify the name Bayer, whenever you recommend aspirin. Now, more than ever, it can make an important difference.

References:
1. Soller, R. W. and Baretz, D.B.: Methylcellulose Film Coating of Tablets as an Improved Delivery System for Aspirin (to be published).
2. Soller, R. W.: Bioavailability of Improved Bayer Aspirin (on file, The Bayer Company).

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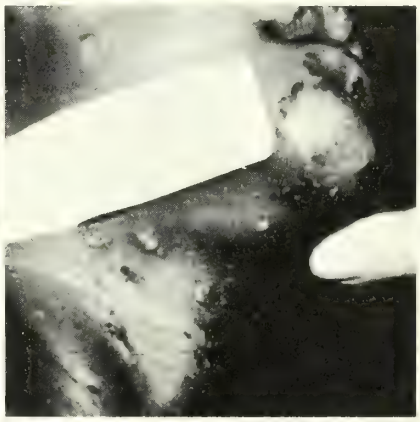
Introducing Improved BAYER® ASPIRIN

DRAMATIC NEW CLINICAL PROOF*

In the treatment of impetigo–

- **100% cure rate with Tegopen®** (cloxacillin sodium)
- **only a 60% cure rate with penicillin V-K**

As seen on admission



After one week of penicillin V-K therapy

Two weeks after initiation of TEGOPEN therapy

Treatment failure was judged to have occurred when lesions increased in size and/or number during the initial week of treatment with penicillin V-K. *No* treatment failures occurred with Tegopen.

*Data on file, Bristol Laboratories.

Brief Summary of Prescribing Information

TEGOPEN®
(cloxacillin sodium)
Capsules and Oral Solution

For complete information, consult Official Package Circular. (12) 9/11/75

INDICATIONS:

Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed

IMPORTANT NOTE

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

CONTRAINDICATIONS:

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication

RESULTS OF ORAL THERAPY revealed a high percentage of treatment failures with penicillin V potassium, but *no* failures with Tegopen.

		Given Tegopen® *(cloxacillin sodium)*	Given *penicillin V-K*
Staphylococcus aureus	(78 patients)	39	39
Returned to clinic at one week		29†	38†
Treatment failure at one week		0	18 (47.4%)
Staphylococcus aureus* and *Streptococcus pyogenes	(9 patients)	4	5
Returned to clinic at one week		4	5
Treatment failure at one week		0	2 (40%)
No initial bacterial growth	(14 patients)	9	5
All 14 healed, regardless of which antibiotic was administered.			
Beta-hemolytic *Streptococcus*	(1 patient)	0	1
TOTALS:	**102 patients**	**52 patients**	**50 patients**

†Eleven patients did not return for their one-week checkup. These were all called by telephone, and their families reported the lesions had healed. One patient was dropped from the study, early, because of adverse reaction to medication

STUDY: DESCRIPTION/PROTOCOL

- 102 nonselected subjects, with initial bacteriology as follows: 77% *Staphylococcus aureus*, 9% mixed *Staphylococcus aureus* and *Streptococcus pyogenes*, and 1% beta-hemolytic *Streptococcus*.‡
- All patients were given randomized therapy—Tegopen capsules or oral solution, or penicillin V-K tablets or oral solution, in recommended dosages according to body weight.
- All patients were evaluated after one week's therapy. If there was no improvement, therapy was switched to the other antibiotic. The "other antibiotic" proved to be Tegopen 100% of the time because no treatment failures had occurred with Tegopen.
- A final assessment of progress was made two weeks after initiation of Tegopen therapy.

‡The remainder, to equal 100%, consisted of 14 patients (13%) who exhibited no initial bacterial growth. These 14 were all healed, whether given Tegopen or penicillin V-K

TEGOPEN®
(cloxacillin sodium)
–effective therapy for staph infections of the skin and skin structures

WARNING:
Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Safety for use in pregnancy has not been established.

PRECAUTIONS:
The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

ADVERSE REACTIONS:
Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

USUAL DOSAGE:
Adults: 250 mg. q.6h.

Children: 50 mg./Kg./day in equally divided doses q.6h. Children weighing more than 20 Kg should be given the adult dose. Administer on empty stomach for maximum absorption.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

SUPPLIED:
Capsules—250 mg. in bottles of 100. 500 mg. in bottles of 100
Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles

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Syracuse, New York 13201

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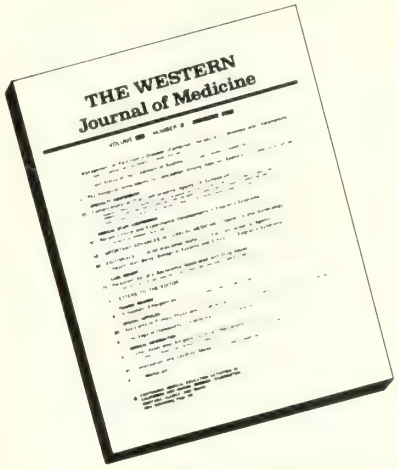

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Pfizer Laboratories Announces

THE FIRST ORAL CALCIUM CHANNEL BLOCKER FOR THE MANAGEMENT OF ANGINA PECTORIS

NEW PROCARDIA® (NIFEDIPINE) *Capsules 10 mg*

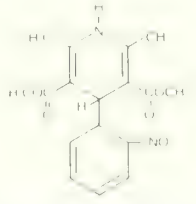
Please see PROCARDIA® *prescribing information on next page.*

PROCARDIA® CAPSULES

For Oral Use

Nifedipine

DESCRIPTION: PROCARDIA (nifedipine) is an antianginal drug belonging to a new class of pharmacological agents, the calcium channel blockers. Nifedipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, $C_{17}H_{18}N_2O_6$, and has the structural formula



Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 346.3. PROCARDIA CAPSULES are formulated as soft gelatin capsules for oral administration each containing 10 mg nifedipine.

CLINICAL PHARMACOLOGY: PROCARDIA (nifedipine) is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. PROCARDIA selectively inhibits calcium ion influx across the cell membrane of cardiac muscle and vascular smooth muscle without changing serum calcium concentrations.

Mechanism of Action: The precise means by which this inhibition relieves angina has not been fully determined, but includes at least the following two mechanisms:

1) Relaxation and prevention of coronary artery spasm: PROCARDIA dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of PROCARDIA in vasospastic (Prinzmetal's or variant) angina. Whether this effect plays any role in classical angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

2) Reduction of oxygen utilization: PROCARDIA regularly reduces arterial pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements and probably accounts for the effectiveness of PROCARDIA in chronic stable angina.

Pharmacokinetics and Metabolism: PROCARDIA is rapidly and fully absorbed after oral administration. The drug is detectable in serum 10 minutes after oral administration, and peak blood levels occur in approximately 30 minutes. It is highly bound by serum proteins. PROCARDIA is extensively converted to inactive metabolites and approximately 80% of PROCARDIA and metabolites are eliminated via the kidneys. The half-life of nifedipine in plasma is approximately two hours. There is no information on the effects of renal or hepatic impairment on excretion or metabolism of PROCARDIA.

Hemodynamics: Like other slow channel blockers, PROCARDIA exerts a negative inotropic effect on isolated myocardial tissue. This is rarely, if ever, seen in intact animals or man, probably because of reflex responses to its vasodilating effects. In man, PROCARDIA causes decreased peripheral vascular resistance and a fall in systolic and diastolic pressure, usually modest (5–10 mm Hg systolic), but sometimes larger. There is usually a small increase in heart rate, a reflex response to vasodilation. Measurements of cardiac function in patients with normal ventricular function have generally found a small increase in cardiac index without major effects on ejection fraction, left ventricular end diastolic pressure (LVEDP) or volume (LVEDV). In patients with impaired ventricular function, most acute studies have shown some increase in ejection fraction and reduction in left ventricular filling pressure.

Electrophysiologic Effects: Although, like other members of its class, PROCARDIA decreases sinoatrial node function and atrioventricular conduction in isolated myocardial preparations, such effects have not been seen in studies in intact animals or in man. In formal electrophysiologic studies, predominantly in patients with normal conduction systems, PROCARDIA has had no tendency to prolong atrioventricular conduction, prolong sinus node recovery time, or slow sinus rate.

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure since severe hypotension can occur from the combined effects of the drugs. See Warnings.

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of PROCARDIA would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. See Warnings.

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents. See Indications and Warnings. Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. In vivo mutagenicity studies were negative.

Pregnancy: Pregnancy category C. Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths, decreased neonatal survival) in rats, mice and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times the maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well-controlled studies in pregnant women. PROCARDIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: In multiple-dose U.S. and foreign-controlled studies in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of PROCARDIA.

Adverse Effect	PROCARDIA (%) (N – 226)	Placebo (%) (N – 235)
Dizziness, light-headedness, giddiness	27	15
Flushing, heat sensation	25	8
Headache	23	20
Weakness	12	10
Nausea, heartburn	11	8
Muscle cramps, tremor	8	3
Peripheral edema	7	1
Nervousness, mood changes	7	4
Palpitation	7	5
Dyspnea, cough, wheezing	6	3
Nasal congestion, sore throat	6	8

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The most common adverse events were the same ones seen in the controlled trials, with dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

Several of these side effects appear to be dose related. Peripheral edema occurred in about one in 25 patients at doses less than 60 mg per day and in about one patient in eight at 120 mg per day or more. Transient hypotension, generally of mild to moderate severity and seldom requiring discontinuation of therapy, occurred in one of 50 patients at less than 60 mg per day and in one of 20 patients at 120 mg per day or more.

In addition, 2% or fewer of patients reported the following: Respiratory: Nasal and chest congestion, shortness of breath. Gastrointestinal: Diarrhea, constipation, cramps, flatulence. Musculoskeletal: Inflammation, joint stiffness, muscle cramps. CNS: Shakiness, nervousness, jitteriness, sleep disturbances, blurred vision, difficulties in balance. Other: Dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving PROCARDIA with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of PROCARDIA treated patients (see Precautions).

In a subgroup of patients with a diagnosis of congestive heart failure as well as angina, dizziness or light-headedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

Laboratory tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gallbladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have already been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

OVERDOSAGE: Although there is no well documented experience with PROCARDIA overdosage, available data suggest that gross overdosage could result in excessive peripheral vasodilation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension due to PROCARDIA overdosage calls for active cardiovascular support including monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Clearance of PROCARDIA would be expected to be prolonged in patients with impaired liver function. Since PROCARDIA is highly protein-bound, dialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION: The dosage of PROCARDIA needed to suppress angina and that can be tolerated by the patient must be established by titration. Excessive doses can result in hypotension.

The starting dose is one 10 mg capsule, swallowed whole, 3 times/day. The usual effective dose range is 10–20 mg three times daily. Some patients, especially those with evidence of coronary artery spasm, respond only to higher doses, more frequent administration, or both. In such patients, doses of 20–30 mg three or four times daily may be effective. Doses above 120 mg daily are rarely necessary. More than 180 mg per day is not recommended.

In most cases, PROCARDIA titration should proceed over a 7–14 day period so that the physician can assess the response to each dose level and monitor the blood pressure before proceeding to higher doses.

If symptoms so warrant, titration may proceed more rapidly provided that the patient is assessed frequently. Based on the patient's physical activity level, attack frequency, and sublingual nitroglycerin consumption, the dose of PROCARDIA may be increased from 10 mg t.i.d. to 20 mg t.i.d. and then to 30 mg t.i.d. over a three-day period.

In hospitalized patients under close observation, the dose may be increased in 10 mg increments over four to six-hour periods as required to control pain and arrhythmias due to ischemia. A single dose should rarely exceed 30 mg.

No "rebound effect" has been observed upon discontinuation of PROCARDIA. However, if discontinuation of PROCARDIA is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close physician supervision.

Co-Administration with Other Antianginal Drugs: Sublingual nitroglycerin may be taken as required for the control of acute manifestations of angina, particularly during PROCARDIA titration. See Precautions, Drug Interactions for information on co-administration of PROCARDIA with beta blockers or long-acting nitrates.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contains 10 mg of nifedipine. PROCARDIA Capsules are supplied in amber glass bottles of 100 capsules (NDC 0069-2600-61).

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

Issued January 1982

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Pfizer LABORATORIES DIVISION
PFIZER INC. NEW YORK, N.Y. 10017

RIMSO®-50
(dimethyl sulfoxide)
50% w/w aqueous solution

INDICATIONS AND USAGE

RIMSO® - 50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. RIMSO ® - 50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.

CONTRAINDICATIONS

None known.

WARNINGS

Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical RIMSO® - 50. The physican should be cognizant of this possibility in prescribing RIMSO® - 50. If anaphylactoid symptoms develop, appropriate therapy should be instituted.

PRECAUTIONS

Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of RIMSO® - 50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation.

Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO® - 50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide.

The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.

DOSAGE AND ADMINISTRATION

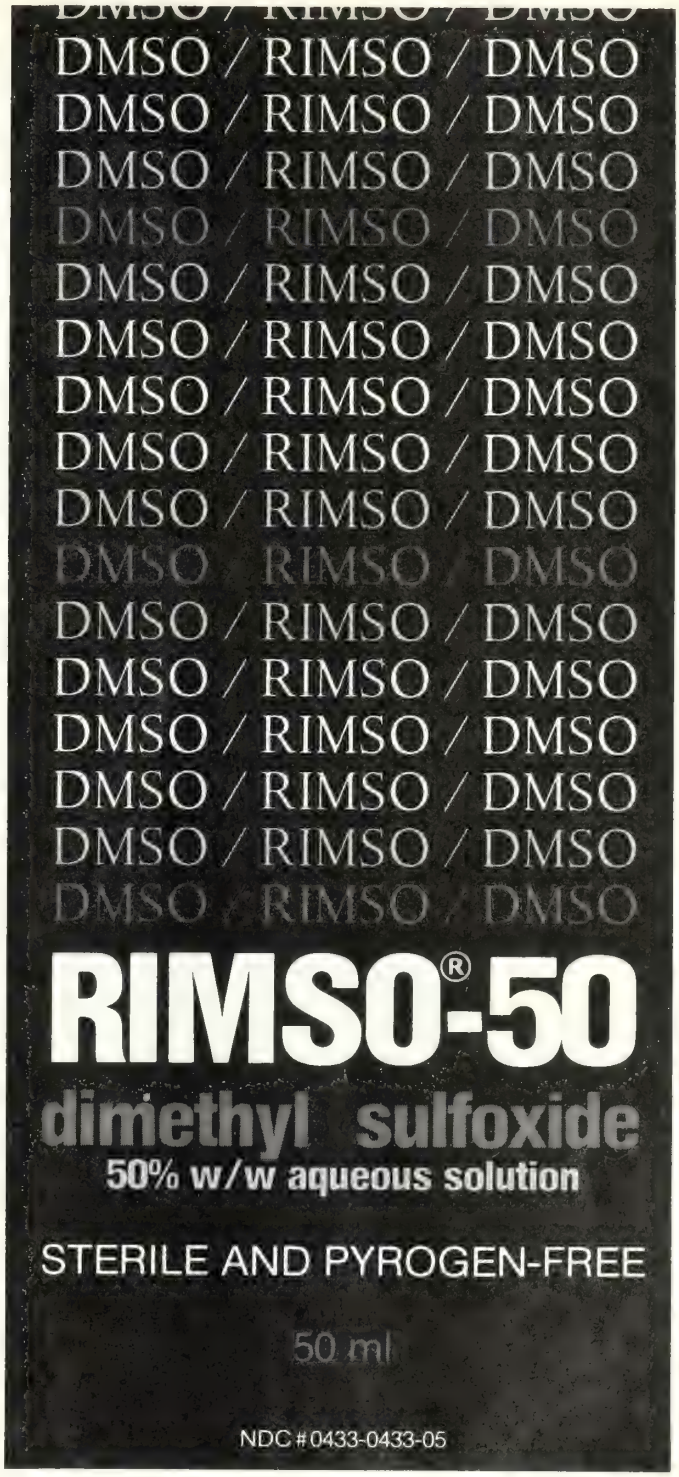
Instillation of 50 ml of RIMSO® - 50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as lidocaine jelly to the uretha is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately.

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO® - 50 can reduce bladder spasm.

In patients with severe interstital cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia. (Saddle block has been suggested).

HOW SUPPLIED

Bottles contain 50 ml of sterile and pyrogen-free RIMSO® - 50 (50% w/w dimethyl sulfoxide aqueous solution).
Dimethyl sulfoxide is clear and colorless.
Protect from strong light.
Store at room temperature (50° to 86°F) (15° to 30°C).
Do not autoclave.
NDC # 0433-0433-05



FOR FURTHER INFORMATION

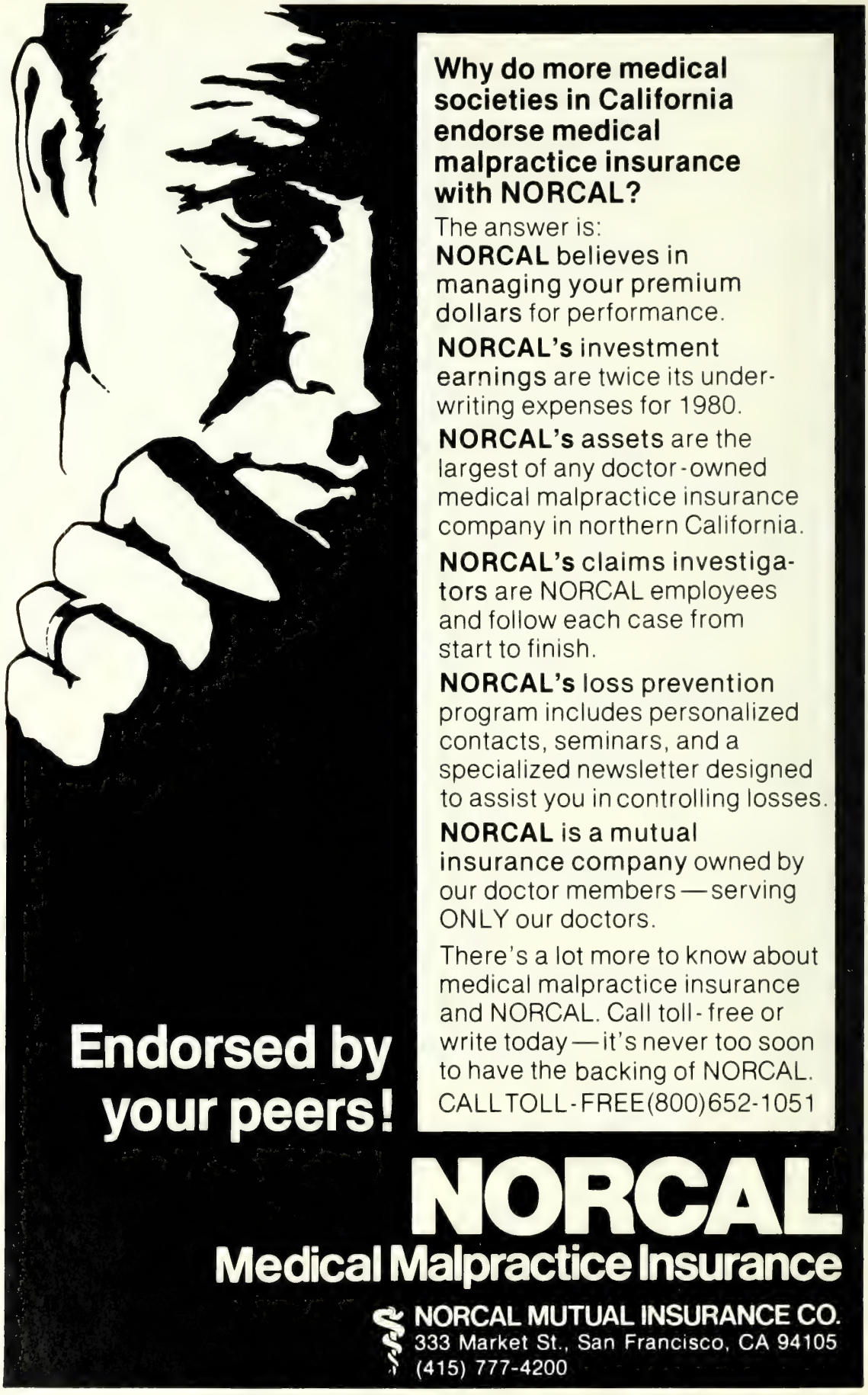
DRS. NAME

ADDRESS

CITY STATE ZIP

SEND TO: RESEARCH INDUSTRIES CORP.
1847 West 2300 South
Salt Lake City, Utah 84119

Toll-Free (800) 453-8432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ANESTHESIOLOGY

March 11-14—**Obstetrical Anesthesia: The State of the Art, 1982.** UCSF at Golden Gateway Holiday Inn, San Francisco. Thursday-Sunday. 13 hrs. $275.

March 14-18—**International Anesthesia Research Society—56th Congress.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: International Anesthesia Research Soc., 3645 Warrensville Center Rd., Cleveland, OH 44122. (216) 295-1124.

March 17-21—**American Society of Regional Anesthesia.** Del Monte Hyatt, Monterey. Wednesday-Sunday. 16 hrs. $175. Contact: Gale Thompson, MD, ASRA, P.O. Box 11083, Richmond, VA 23230. (804) 358-0305.

March 21-26—**Anesthesiology 1982—8th Annual Winter Meeting.** Anesthesiology Educational Foundation at Sierra Nevada Inn, Mammoth Lakes. Sunday-Friday. Contact: AEF, P.O. Box 24230, Los Angeles 90024.

April 3-10—**10th Obstetric Anesthesia Conference.** Dept. of Anesthesiology, Ohio State Univ. College of Medicine, at Sheraton Waikiki, Oahu, Hawaii. One week. 25 hrs. Contact: Dept. of Anesthesiology, c/o Bradford Travel, 1200 W. Henderson Rd., Columbus, OH 43220. (614) 457-9990 or (614) 421-8487 (OSU).

April 26-30—**6th Annual Hawaiian Seminar on Clinical Anesthesiology.** Calif. Society of Anesthesiologists at Maui Surf Hotel, Maui. Monday-Friday. 20 hrs. Contact: Educational Programs Div., CSA, 100 E. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

May 22-23—**Hemodynamic Monitoring/Pulmonary Artery Catheterization—Hands-on Workshops.** Calif. Soc. of Anesthesiologists and Stanford at Stanford. Saturday-Sunday. 15 hrs. $275, CSA members; $325, nonmembers. Contact: Educational Prog. Div., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

June 10-13—**California Society of Anesthesiologists—Annual Meeting.** Town and Country, San Diego. Thursday-Sunday. Contact: Educational Prog. Div., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

June 24-26—**Practical Closed Circuit Anesthesia II.** Pacific Medical Center at Hyatt at Union Square, San Francisco. Thursday-Saturday. 17 hrs. $300. Contact: Office of Cont. Ed., PMC, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

August 21-22—**Hemodynamic Monitoring/Pulmonary Artery Catheterization—Hands-on Workshops.** Calif. Soc. of Anesthesiologists and Stanford at Stanford. Saturday-Sunday. 15 hrs. $275, CSA members; $325, nonmembers. Contact: Educational Prog. Div., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

CANCER

February 17—**Advances in Cancer Detection.** Hospital of the Good Samaritan at Biltmore Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Bonnie VanWaardenburg, Cancer Symp., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

February 24-26—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF. Wednesday-Friday.

February 27-28—**Breast Cancer: Conservation Surgery and Radiation Therapy Now—17th Annual San Francisco Cancer Symposium.** West Coast Cancer Fndn.; Am. Cancer Soc., Calif. Div.; St. Mary's Hosp. and Med. Ctr. at Sheraton Fisherman's Wharf, San Francisco. Saturday-Sunday. 12 hrs. $115 before Jan. 1; $140, thereafter. Contact: West Coast Cancer Fndn., 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

March 25-27—**Western States Conference on Cancer Rehabilitation: Psychosocial, Physical and Economic Interventions.** No. Calif. Cancer Prog.; Am. Cancer Soc., Calif. Div.; UCLA Jonsson Comprehensive Cancer Ctr.; L.A. Co.-USC Comprehensive Cancer Ctr.; Community Cancer Control-

(Continued on Page 25)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

When she can't manage, you can.

The sweats. The hot flushes. The distress and discomfort of atrophic vaginitis. The possibility of osteoporosis.* The menopause.

For many women, it's a time of confusion and frustration. Counseling can help her overcome these feelings. But counseling can't stop moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard bone loss*... the true signs of estrogen deficiency. And that's where she needs you most.

You're an expert at estrogen replacement. You know why it should be used. When it's best avoided. That it's not intended to treat nervous symptoms or depression associated with the menopause. That it can be very helpful in treating symptoms related to estrogen deficiency. You know how to cycle therapy. Determine dosage. Check for contraindications and possible complications. Follow-up. You know when therapy should begin, and when it deserves to end.

Most of all, you know your patient—and when she really needs the effective relief you can give her with PREMARIN.

When it comes to managing the estrogen-deficiency symptoms of the menopause, you've got what it takes.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

Prescribed with care by physicians who care.

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg/0.625 mg/1.25 mg/2.5 mg

Please see following page for Brief Summary of Prescribing Information.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1 ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year[1-3] This risk was independent of the other known risk factors for endometrial cancer These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade [4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4 5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose [3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration,[3] it therefore appears prudent to utilize such a regimen Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses

2 ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare[5,6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4 7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000 In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U.S.P) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows

Effective:

1 Moderate to severe *vasomotor* symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions)

2 Atrophic vaginitis

3 Kraurosis vulvae

4 Female hypogonadism

5 Female castration

6 Primary ovarian failure

7 Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease

8 Prostatic carcinoma—palliative therapy of advanced disease

9 Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures Final classification of this indication requires further investigation

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen dependent neoplasia 3 Known or suspected pregnancy (See Boxed Warning) 4 Undiagnosed abnormal genital bleeding 5 Active thrombophlebitis or thromboembolic disorders 6 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy)

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility.[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users [31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives.[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives [36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression [23a] Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use The pathologist should be advised of estrogen therapy when relevant specimens are submitted If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete

The following changes may be expected with larger doses of estrogen

a Increased sulfobromophthalein retention

b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3; increased norepinephrine-induced platelet aggregability

c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered

d Impaired glucose tolerance

e Decreased pregnanediol excretion

f. Reduced response to metyrapone test

g Reduced serum folate concentration

h Increased serum triglyceride and phospholipid concentration

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives. breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome, amenorrhea during and after treatment; increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome, tenderness, enlargement, secretion (of breasts), nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued, erythema multiforme; erythema nodosum, hemorrhagic eruption; loss of scalp hair, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: 1 *Given cyclically for short term use only* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0 3 to 1 25 mg or more daily)

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (*e g.* three weeks on and one week off)

Attempts to discontinue or taper medication should be made at three to six month intervals

2 *Given cyclically* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis

Female hypogonadism—2.5 to 7 5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration If bleeding does not occur by the end of this period, the same dosage schedule is repeated The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U S P), 2.5 to 7.5 mg daily in divided doses, for 20 days During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding

Female castration and primary ovarian failure—1.25 mg daily, cyclically Adjust upward or downward according to response of the patient For maintenance, adjust dosage to lowest level that will provide effective control

Osteoporosis (to retard progression)—1 25 mg daily, cyclically

3 *Given for a few days* Prevention of postpartum breast engorgement—3 75 mg every four hours for five doses, or 1 25 mg every four hours for five days

4 *Given chronically* Inoperable progressing prostatic cancer—1 25 to 2 5 mg three times daily

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S P) No 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000 No 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No. 868—Each *green* tablet contains 0 3 mg in bottles of 100 and 1,000

PHYSICIAN REFERENCES: 1 Ziel, H.K., *et al.*: N. Engl J Med. *293*:1167-1170, 1975 2. Smith, D.C., *et al.*: N Engl J Med *293*:1164-1167, 1975 3 Mack, TM, *et al.*: N Engl J Med *294*:1262-1267, 1976 4 Weiss, N.S., *et al.*: N. Engl J. Med *294*:1259-1262, 1976. 5 Herbst, A.L., *et al.*: N. Engl. J Med *284*:878-881, 1971 6 Greenwald, P, *et al.*: N. Engl J. Med. *285*:390-392, 1971. 7. Lanier, A., *et al.* Mayo Clin. Proc *48*:793-799, 1973 8 Herbst, A., *et al* Obstet Gynecol *40*:287-298, 1972 9 Herbst, A., *et al.*: Am J Obstet Gynecol *118*:607-615, 1974 10 Herbst, A., *et. al.*: N Engl J Med *292*:334-339, 1975 11 Stafl, A., *et al.*: Obstet Gynecol *43*:118-128, 1974. 12 Sherman, A I, *et al.*: Obstet Gynecol *44*:531-545, 1974 13 Gal, I., *et al.*: Nature *216*:83, 1967 14. Levy, E P, *et al.*: Lancet *1*:611, 1973. 15. Nora, J., *et al.*: Lancet *1*:941-942, 1973. 16 Janerich, D.T., *et al* N. Engl J Med *291*:697-700, 1974 17. Boston Collaborative Drug Surveillance Program. N. Engl. J. Med *290*:15-19, 1974. 18 Hoover, R., *et al.*: N. Engl. J Med *295*:401-405, 1976 19 Daniel, D. G., *et al.*: Lancet *2*:287-289, 1967 20 The Veterans Administration Cooperative Urological Research Group: J. Urol *98*:516-522, 1967 21 Bailar, J.C. Lancet *2*:560, 1967 22 Blackard, C., *et al.*: Cancer *26*:249-256, 1970 23 Royal College of General Practitioners: J.R Coll Gen Pract *13*:267-279, 1967 23a Royal College of General Practitioners. Oral Contraceptives and Health, New York, Pitman Corp., 1974 24 Inman, W.H.W., *et al* Br Med J. *2*:193-199, 1968 25 Vessey, M.P, *et al.*: Br Med J *2*:651-657, 1969 26 Sartwell, P.E., *et al* Am. J Epidemiol. *90*:365-380, 1969 27 Collaborative Group for the Study of Stroke in Young Women: N Engl J Med *288*:871-878, 1973 28 Collaborative Group for the Study of Stroke in Young Women: J A M A *231*:718-722, 1975 29 Mann, J.I., *et al.*: Br Med. J. *2*:245-248, 1975 30 Mann, J I., *et al* Br Med. J. *2*:241-245, 1975. 31 Inman, W.H.W., *et al.*: Br Med J. *2*:203-209, 1970 32 Stolley, P.D., *et al.*: Am. J. Epidemiol *102*:197-208, 1975 33. Vessey, M.P., *et al.*: Br Med J. *3*:123-126, 1970. 34. Greene, G R., *et al.*: Am J. Public Health *62*:680-685, 1972. 35 Coronary Drug Project Research Group J A M A *214*:1303-1313, 1970 36 Mays, E.T., *et al.*: J A M A *235*:730-732, 1976. 37 Pfeffer, R.I. *et al.*: Am. J. Epidemiol *103*:445-456, 1976

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L.A.; S.F. Regional Cancer Fndn. at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: Carrie Ewing, No. Calif. Cancer Prog., P.O. Box 10144, Palo Alto 94303. (415) 497-7431.

April 2-7—**Hematology/Oncology Update.** See Medicine, April 2-7.

April 3—**Oncology Update 1982.** Northridge Hospital Medical Center at Biltmore Hotel, Los Angeles. Saturday. 8 hrs. $125. Contact: Sandra Rozzen, Med. Ed. Dept., NHMC, 18300 Roscoe Blvd., Northridge 91328. (213) 885-5311.

April 22-24—**Bladder Cancer.** American Urological Assn. at Biltmore Hotel, Los Angeles. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, AUA Office of Education, P.O. Box 25147, Houston, TX 77005.

EMERGENCY MEDICINE

February 20—**Trauma Radiology for the Emergency Practitioner.** Calif. Chap., American College of Emergency Physicians, at St. Mary Medical Center, Long Beach. Saturday. 8 hrs. $75. ACEP members; $95, nonmembers. Contact: CAL/ACEP, 8639 Lincoln Blvd., Suite 240, Los Angeles 90045. (213) 776-1820.

February 28-March 5—**Emergency Medicine.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

March 7-10—**Sports Injuries Update.** UCD at Hyatt, Lake Tahoe. Sunday-Wednesday.

March 14-19—**Third Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Lakes. Sunday-Friday. 25 hrs. $290. Contact: Medical Conferences, Inc., P.O. Box 52-B, Newport Beach 92662. (714) 540-9876.

March 15-19—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Islandia Hotel, San Diego. Monday-Friday. 36 hrs. $425.

April 10-17—**Pediatric Emergencies.** UCSD at Kauai, Hawaii. One week. 21 hrs. $325.

April 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, Inc., 2310 Mason St., San Francisco 94133.

April 24-May 2—**Emergency Medicine.** USC at Hawaii. One week. 25 hrs. $425.

May 10-14—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD. Monday-Friday. 36 hrs. $425.

June 7-11—**Postgraduate Institute for Emergency Room Physicians—Symposium III.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs. $425.

June 28-July 2—**Topics in Emergency Medicine.** UCSF. Monday-Friday. 35 hrs. $350.

July 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, Inc., 2310 Mason St., San Francisco 94133.

August 9-13—**Postgraduate Institute for Emergency Room Physicians—Symposium II.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs.

MEDICINE

February 16-19—**Clinical Investigation.** See Of Interest to All, February 16-19.

February 17-19—**Recent Advances in Noninvasive Cardiac Imaging: Applications in the Diagnosis and Management of Ischemic Heart Disease.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

February 18-20—**Controversies and Problem Solving With Endoscopy—An Update.** So. Calif. Society for Gastrointestinal Endoscopy at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 18 hrs. Contact: Dr. Albert Dreskin, 13652 Cantara St., Panorama City 91402.

February 20-27—**Cardiology.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 21-23—**Recent Advances in Clinical Endocrinology.** UCSF. Sunday-Tuesday.

February 24-25—**American College of Physicians—Regional Meeting.** Hilton, Beverly Hills. Wednesday-Thursday. Contact: Mitchel D. Covel, MD, 9730 Wilshire Blvd., Beverly Hills 90212.

February 25-28—**Federation of the Western Societies of Neurological Science.** Hotel del Coronado, Coronado. Thursday-Sunday. 15 hrs. Contact: Renee Kaseff, 525 Hurlingham Ave., San Mateo 94402. (415) 344-9082.

February 26—**A Day in Nephrology.** Sutter Community Hospitals at Holidome Convention Center, Sacramento. Friday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

February 26-27—**American College of Physicians—Regional Meeting.** Doubletree Inn, Monterey. Friday-Saturday. Contact: Jerry P. Lewis, MD, 618 Francisco Place, Davis 95616.

February 26-28—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Aladdin Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

February 27-28—**Immunology.** STAN. Saturday-Sunday. 12 hrs. $225.

February 27-28—**Basic Neuroscience.** STAN. Saturday-Sunday. 12 hrs. $225.

February 27-28—**Asthma: Impact and Strategies for Change.** UCLA. Saturday-Sunday. 14 hrs. $85.

March 3-6—**Third World Congress for Bronchology.** World Assn. for Bronchology and American College of Chest Physicians at Town and Country, San Diego. Wednesday-Saturday. $250, WAB and ACCP members; $300, nonmembers. Contact: ACCP, P.O. Box 93826, Chicago 60670. (312) 698-2200.

March 3-6—**Immunology and the Clinical Practice of Allergy—6th Annual Course.** UCSD at Hilton Hotel, San Diego. Wednesday-Saturday. 20 hrs.

March 3-6—**Third World Congress for Bronchology.** American College of Chest Physicians and World Assn. for Bronchology at Town and Country Hotel, San Diego. Wednesday-Saturday. $250, ACCP and WAB members; $300, nonmembers. Contact: ACCP, P.O. Box 93826, Chicago 60670. (312) 698-2200.

March 5—**Diabetes.** UCD at Red Lion Inn, Sacramento. Friday.

March 7-10—**Basic Cardiology for the Practicing Physician.** UCSF at Lake Tahoe. Sunday-Wednesday.

March 10—**Hypothyroidism—Unmasked.** LLU. Wednesday. 4 hrs. $30.

March 12-13—**Exercise Stress Testing: Today and Tomorrow.** American College of Cardiology at Memorial Hospital Medical Center, Long Beach. Friday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

March 12-13—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

March 12-14—**Western Institute on Epilepsy.** UCLA at Marriott, Los Angeles. Friday-Sunday. $60.

March 13-20—**Reproductive Endocrinology.** USC at Maui. One week. $395.

(Continued on Page 29)

SPOT-RESISTANT ORAL CONTRACEPTION IS HERE!

It's LO/OVRAL 30. And here's how it holds spotting and breakthrough bleeding to a minimum: Hormone balance right from the start...and throughout the cycle. Hormone balance made possible with a very low dose oral contraceptive because of the supportive progestational activity of norgestrel, Wyeth's exclusive progestogen.

Regular withdrawal bleeding, too despite its low dose. In clinical trials amenorrhea—defined as absence of bleeding in the 7 pill-free days—was reported in only 2.1% of total cycles. And when defined as absence of bleeding for 60 days or more (as it often is), the incidence was only 0.2%.*

And comfort for most patients* thanks to the same balance that helps prevent spotting and breakthrough bleeding. In the clinical trials, most patients stayed free of common side effects such as nausea (0.6% of cycles), vomiting (0.1%), depression (0.5%) and acne (0.9%).

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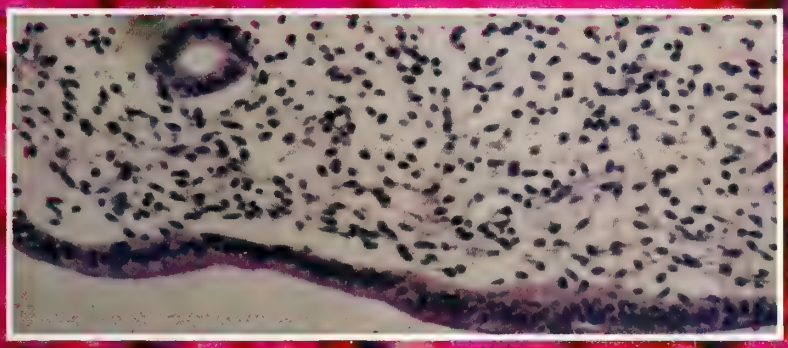
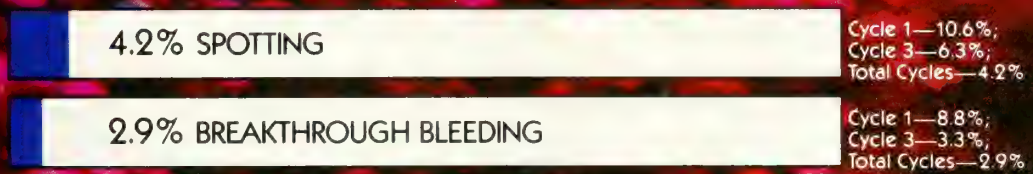


LO/OVRAL—1st cycle
Biopsy of intact endometrium in stable, progestogen suppressed state. Small, tubular gland in loose stroma without hemorrhage, fragmentation or debris characteristic of desquamating endometrium.

Even in the first cycle, the effective action of LO/OVRAL on the endometrium, such as you see here, provides the resistance against spotting and breakthrough bleeding you hope to achieve.

HISTOLOGICALLY... AND CLINICALLY.



A near-spotless record— in clinical trials involving 22,489 cycles*

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. Contraindications, Warnings, Precautions, Adverse Reactions, etc., in the accompanying In Brief should be carefully considered.

See full prescribing information.

LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth

...with a near-spotless record!

See important information on following page.

IN BRIEF:

Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3. Cerebral-vascular or coronary-artery disease.
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of unoerlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000, ages 35-44—33/100,000, ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately

A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency

9. The pathologist should be advised of OC therapy when relevant specimens are submitted

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline

Carcinogenesis—See Warnings on carcinogenic potential of OC's

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females

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(Continued from Page 25)

March 19-20—**Non-Invasive Cardiology Conference.** Claremont Community Hospital at Sheraton Harbor Island Hotel, San Diego. Friday-Saturday. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

March 21-24—**Dermatology Consultants' Course.** UCSF at Yosemite. Sunday-Wednesday.

March 22-April 2—**30th Annual Review of Internal Medicine.** USC. 12 days.

March 26-28—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

March 29-April 2—**Management of Coronary Heart Disease: Medical, Surgical, Exercise.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs.

April-June—**Allergy/Immunology for the Practicing Internist.** UCLA. Wednesday evenings.

April 1-3—**Asthma Update—1982.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Saturday. 19 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 1-4—**Principles in the Practice of Allergic Diseases in Adults and Children.** UCD at Del Monte Hyatt, Monterey. Thursday-Sunday.

April 2-7—**Hematology/Oncology Update.** UCD at Ahwahnee Hotel, Yosemite. Friday-Wednesday.

April 3—**Cardiology Update for the Practicing Physician.** American Heart Assn.-Greater Los Angeles Affiliate, San Gabriel Valley Division, at Huntington Sheraton, Pasadena. Saturday. 8 hrs. $55, members; $70, nonmembers. Contact: Gary L. Kossky, AHA, 929 N. Grand Ave., Covina 91724. (213) 339-7382 or (213) 686-2506.

April 14—**Cardiology Update 1982.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

April 16—**Injectable Collagen—Applications and Technique.** STAN. Friday. $100. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

April 16-17—**Recent Advances in Renal, Metabolic and Endocrine Disorders.** St. Francis Medical Center at Bonaventure Hotel, Los Angeles. Friday-Saturday. $115. Contact: Allan M. Hoffman, EdD, Dir., Med. Ed., St. Francis Med. Ctr., 3630 E. Imperial Highway, Lynwood 90262. (213) 603-6171.

April 16-18—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

April 22-23—**Infectious Disease Symposium.** Epidemiology Assn. of Greater Sacramento and Mercy Hospital at Red Lion Inn, Sacramento. Thursday-Friday. 14 hrs. Contact: Office of Cont. Med. Ed., Mercy General Hospital, 4001 J St., Sacramento 95819. (916) 453-4545.

April 25-28—**Dermatology.** UCD at Ahwahnee Hotel, Yosemite. One week.

April 28—**Thyroid '82.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Bonnie VanWaardenburg, Coordinator of Symposia, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

May 6-7—**Advances in Infectious Diseases.** UCSF. Thursday-Friday. 14 hrs. $170.

May 7-8—**Common Nervous System Pathology Diagnosis and Treatment.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 14 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 7-9—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

May 15-18—**American Thoracic Society—Annual Scientific Meeting.** Bonaventure Hotel, Los Angeles. Saturday-Tuesday. 30 hrs. $35, members; $100, nonmembers. Contact: S. R. Iannotta, Exec. Dir., ATS, 1740 Broadway, New York 10019. (212) 245-8000.

May 17-21—**Advances in Internal Medicine.** UCSF. Monday-Friday. 40 hrs. $375.

May 21-22—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

May 27-30—**4th Annual Refresher Course in Allergy and Asthma.** UCD at Marriott's Great America, Santa Clara. Thursday-Sunday.

June 7-9—**Clinical Echocardiography—1982: M-Mode, 2-Dimensional and Pulse Doppler Techniques.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Monday-Wednesday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 9—**Bleeding Disorders.** LLU. Wednesday. 4 hrs. $30.

June 11-13—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Aladdin Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

June 25-27—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Newporter Inn, Newport Beach. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

July 16-17—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

July 17-24—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 21 hrs. $325.

August 6-8—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Clouds-Cal Neva Resort, Lake Tahoe. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 13-15—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 20-22—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at Hyatt, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 30-September 4—**Fifth Comprehensive Nephrology Review Course.** UCLA at Marriott, Los Angeles. Monday-Saturday. 28½ hrs. $595.

OBSTETRICS AND GYNECOLOGY

March 13-20—**Reproductive Endocrinology, Infertility and Contraception.** See Of Interest To All, March 13-20.

March 14-17—**OB/GYN for the Practicing Physician.** UCSF at Yosemite. Sunday-Wednesday.

(Continued on Page 45)

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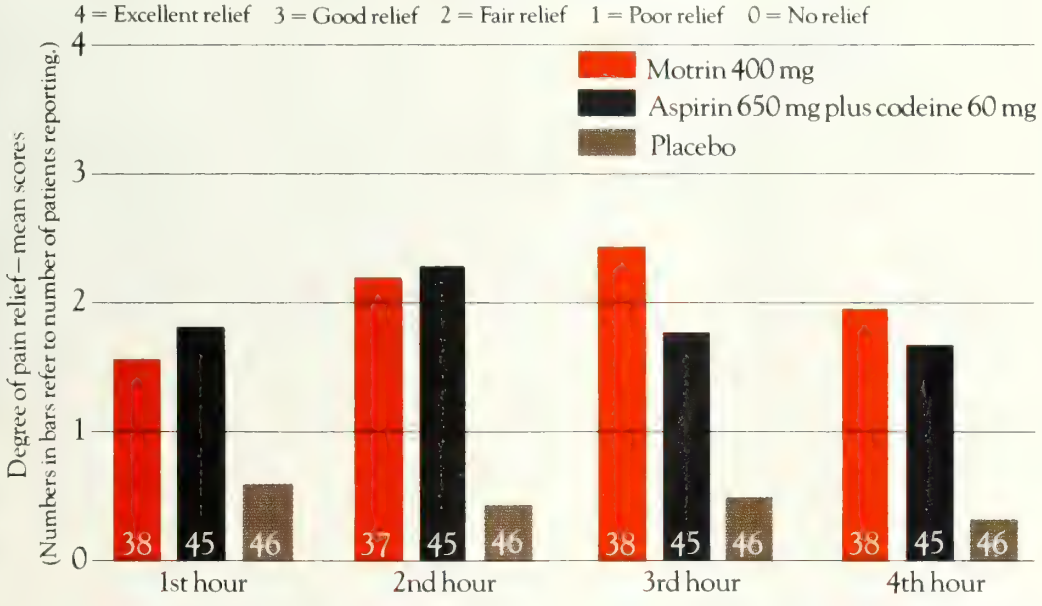

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Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin:* Used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy nor by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal (4% to 16%). This includes nausea;* epigastric pain;* heartburn;* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness;* headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis, including flares of chronic disease: Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for relief of pain.

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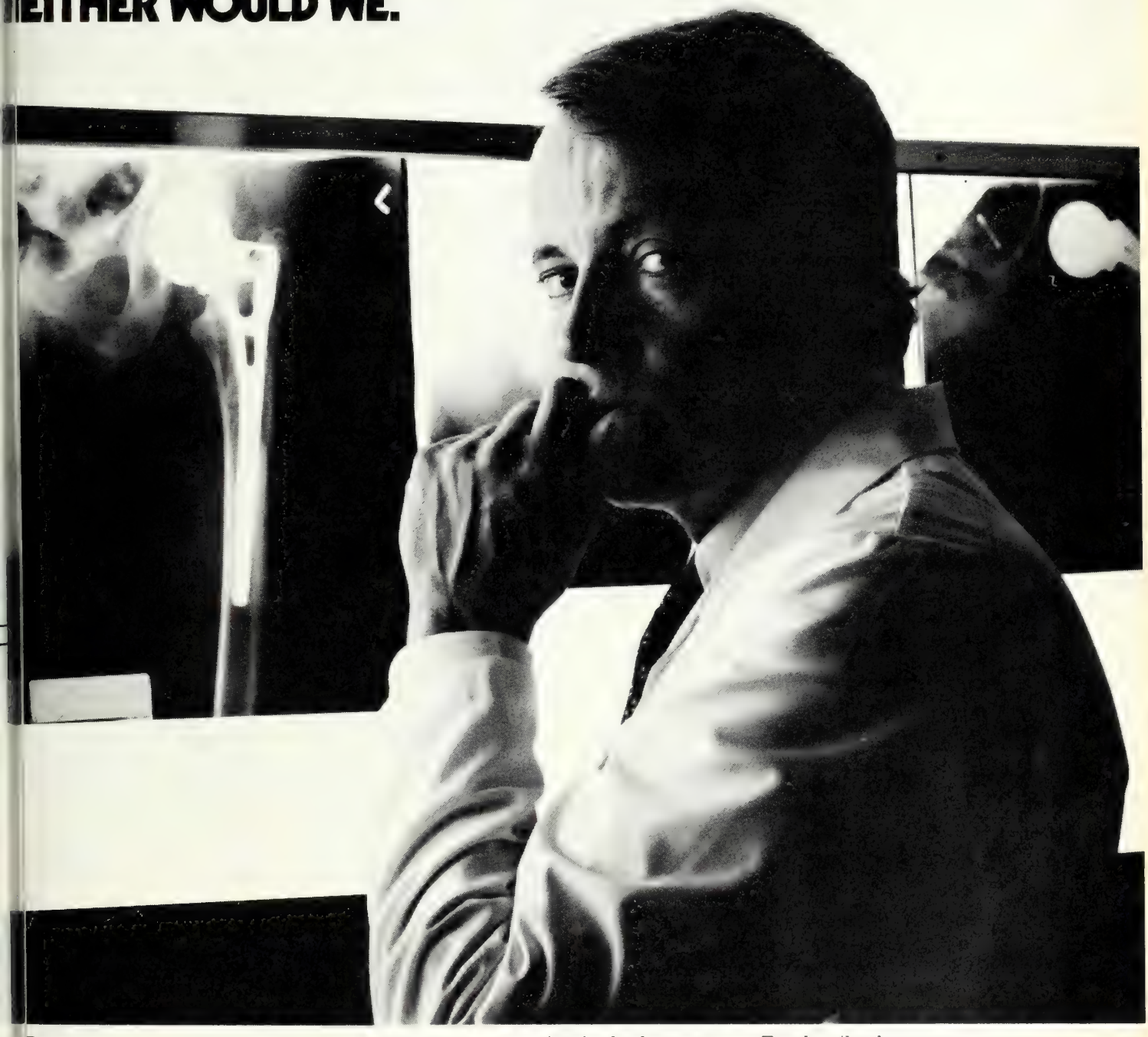

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This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Watch for signs of impending coma in severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia have been reported with thiazides. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide', although a causal relationship has not been established

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THE WESTERN
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Refer to: Akl BF, Talbot W, Neal JF, et al: Noncardiac operations after coronary revascularization. West J Med 136: 91-94, Feb 1982

Noncardiac Operations After Coronary Revascularization

BECHARA F. AKL, MD; WILLIAM TALBOT, MD; JOE F. NEAL, MD, *and* DENNIS HAVENS, MD, *Albuquerque*

In 35 patients who had had earlier myocardial revascularization, a total of 44 noncardiac operations under general or spinal anesthesia were carried out. There was one cardiac death and three postoperative complications. Compared with the risk of general anesthesia and noncardiac surgical procedures in patients with coronary artery disease who have not had coronary revascularization, this is a major improvement. We conclude that myocardial revascularization provides significant protection against the risk of cardiac complications and death for patients with ischemic heart disease in whom general anesthesia and noncardiac procedures are needed.

WITH PROGRESSIVELY MORE patients undergoing coronary revascularization, and with the life expectancy of patients with severe ischemic heart disease increased because of coronary revascularization, we are encountering more patients with previous aortocoronary bypass in whom noncardiac operations are needed. Because arteriosclerosis is a generalized cardiovascular disease, it is not surprising that other vascular procedures such as abdominal aortic aneurysms, aortofemoral and carotid procedures constitute a large number of the secondary procedures required. The need for nonvascular abdominal, urological and intrathoracic procedures also is being encountered with increasing frequency in an ever growing population with previous myocardial revascularization. This retrospective analysis was done in an attempt to assess the risk or safety of noncardiac procedures in patients who have had myocardial revascularization.

From the Division of Thoracic and Cardiovascular Surgery, University of New Mexico School of Medicine and the Veterans Administration Medical Center, Albuquerque.

Submitted August 10, 1981.

Reprint requests to: Bechara F. Akl, MD, Department of Surgery, University of New Mexico School of Medicine, Albuquerque, NM 87131.

Patients

All patients with prior coronary revascularization undergoing noncardiac operations under general or spinal anesthesia at the University of New Mexico Hospital and the Veterans Administration Medical Center in Albuquerque during the period of July 1976 to December 1980 were included. Procedures carried out under local anesthesia and diagnostic procedures were not included. Patients in whom a secondary procedure was done to treat a complication of the cardiac operation in the immediate postoperative period—such as mediastinitis, acute cholecystitis or acute pancreatitis—were also excluded from this review. Thirty-five patients ranging in age from 36 to 70 years (mean 55.9 years) were included. There were 33 men and 2 women. They underwent a total of 44 noncardiac operations (6 patients had more than one secondary operation). Eleven patients had a history of chronic hypertension.

Thirteen patients were more than 60 years of age. Twenty-four patients had significant three-vessel coronary artery disease. The interval from coronary revascularization to secondary operation was six days to 48 months (mean 11.63 months). The myocardial revascularization consisted of one to five vessels (mean 3.05 vessels) aortocoronary bypass. In addition, two patients had aortic valve replacements and two patients had left ventricular aneurysm resections. The 44 secondary procedures in the 35 patients were distributed as shown in Table 1. Four procedures were done under spinal anesthesia and the rest under general anesthesia.

TABLE 1.—*Distribution of 44 Secondary Procedures in 35 Patients Who Had Had Myocardial Revascularization*

Intra-abdominal vascular procedures	11
Intra-abdominal nonvascular procedures	12
Peripheral vascular procedures	10
Others (intrathoracic, urological and surface procedures)	11

Results

There were two deaths related to the operations. One was presumed to be cardiac in origin. In a 49-year-old man a cholecystectomy was carried out for subacute cholecystitis three months after coronary revascularization. Four days postoperatively, during what appeared to be a satisfactory course, he had a cardiac arrest while walking. He could not be resuscitated. At autopsy the aortocoronary grafts were found to be patent and there was no evidence of recent myocardial infarctions or pulmonary emboli. His death was presumed to be secondary to an episode of arrhythmia. The other death was thought to be noncardiac in origin. A 64-year-old woman had an aortic valve replacement and a two-vessel coronary revascularization. She was a patient with steroid-dependent rheumatoid arthritis. Fifteen months after her cardiac operation she underwent a laparotomy with colostomy for a perforated rectum. An intra-abdominal abscess developed and the patient died one week later from sepsis.

Three complications occurred. One pulmonary embolus responded to standard anticoagulant therapy. In one patient supraventricular tachyarrhythmia was controlled with medical therapy and in another a superficial thrombophlebitis developed which responded to standard nonoperative treatment.

Discussion

The high incidence of cardiac complications in patients with ischemic heart disease undergoing surgical procedures under general anesthesia has been documented in several reports. Steen and co-workers[1] reviewing the cases of 587 patients with previous infarctions found an incidence of reinfarction of 6.1 percent with general anesthesia. Sixty-nine percent of these reinfarctions were fatal. Risk factors associated with the highest incidence of reinfarctions were thoracic and upper abdominal procedures, time under anesthesia, hypotensive episodes during operation and preoperative hypertension. Several reports[2-5] reviewing more specifically the results of abdominal aortic aneurysm resections also documented a high incidence of fatal myocardial infarctions in patients with histories of ischemic heart disease. Fatal myocardial infarction was the leading cause of early death in these series. This high incidence of cardiac complications following abdominal aortic aneurysm resections is not surprising because these patients are more likely to have the high risk factors delineated in Steen's report.[1] The incidence of myocardial infarctions with other procedures also remains higher than normal for patients with known coronary artery disease undergoing carotid endarterectomies, aorto-iliac reconstruction for occlusive disease and other procedures.[6,7]

Considering the patient population that forms the basis of this report, a preponderance of men older than 50 years with a large number of heavy smokers and hypertensive patients with known ischemic heart disease, we believe the mortality of one cardiac death in 44 procedures (2.4 percent) and the complication rate of 3 of 44 (6.8 percent) is very encouraging and reflects the protection afforded by their previous coronary revascularization. These findings are not unique. Crawford and co-workers[8] reported a mortality of 1.1 percent in 358 patients undergoing noncardiac procedures after an earlier coronary artery bypass. They noted a higher medical complication rate if the secondary procedure was carried out less than 30 days after coronary artery bypass. They also noted that the long-term survival after carotid endarterectomy was better for those patients with a previous coronary artery bypass than for patients with known coronary artery disease and no prior bypass (88 percent three-year survival

versus 73 percent). Ennix and associates[9] reporting on 1,238 patients seen consecutively between 1967 and 1977 noted a 3 percent mortality in 135 patients undergoing carotid endarterectomy with simultaneous coronary artery bypass or following coronary artery bypass, whereas 18.2 percent (14 of 77 patients) of patients with known coronary artery disease without the benefit of a coronary bypass died following carotid endarterectomy. Mahar and co-workers[7] studying two similar groups of patients reported no postoperative myocardial infarctions or cardiac mortality in 99 patients with previous coronary artery bypass operations. In 49 patients with known coronary artery disease but no prior revascularization, there were three myocardial infarctions and one death from cardiac causes. In the group of patients with three-vessel coronary artery disease without previous coronary artery bypass, the rate of myocardial infarction was approximately 20 percent following general anesthesia. In our group of patients there were 24 patients with severe three-vessel coronary artery disease. There were no documented postoperative infarctions and one cardiac-related death.

Considering this significant reduction of cardiac complication rates and the progressive decline of the incidence of complications following coronary angiography and aortocoronary bypass, some authors have recommended routine coronary angiography in every patient before elective resection of abdominal aortic aneurysm and aorto-iliac reconstruction.[10] Coronary artery bypass was then done as a preparation for noncardiac operations in selected patients and has resulted in a significant reduction of risk. Whether or not this approach is necessary in every patient is not certain. It would seem appropriate in patients with known coronary artery disease (by history or symptoms or abnormal electrocardiogram) and probably appropriate in patients needing abdominal aortic aneurysm resection.

Even though we do not routinely follow this recommendation in asymptomatic patients, a few of our patients were in this category and coronary angiography and coronary artery bypass were done as a preparation for other major elective procedures. One illustrative example is a 64-year-old man who presented with progressive angina after a previous myocardial infarction. On cardiac catheterization he was found to have severe three-vessel disease. An incidental finding of a physical examination done at admission was a rectal mass that proved to be adenocarcinoma. The risk of an abdominoperineal resection in this patient with severe three-vessel coronary artery disease and progressive angina was considered high. Consequently a four-vessel coronary revascularization was carried out as a preparation. Because of the malignant nature of his other lesion we elected to proceed with abdominoperineal resection without much delay. This was done three weeks later without complication. For purely elective procedures, however, we agree with Crawford's recommendation[8] for a three months' delay because in his extensive review he documented a higher incidence of medical complications when the secondary procedure was done after a shorter interval.

In patients with no evidence of ischemic heart disease undergoing carotid endarterectomy, peripheral vascular operations or other surface procedures, the risk is reasonable with proper anesthetic and postoperative management.[11,12] The fact that their long-term survival is improved with the addition of coronary artery bypass[8,12] should probably be taken on its own merit and included in the progressively changing indication for coronary artery bypass but not necessarily as a protective step before a vascular procedure. Patients without evidence of ischemic heart disease needing aorto-iliac reconstruction for occlusive disease probably fall between these two categories and treatment should be determined based on the other risk factors involved.

Noninvasive assessment and stress testing, when possible, may be a reasonable alternative to coronary angiography in patients at risk.[10,13,14] Unfortunately, the inability of some patients to complete adequate exercise testing as well as the false positive and false negative results continue to be a drawback to the noninvasive testing available.

Even with the protection provided by a previous myocardial revascularization the anesthetic management of these patients should follow the same principles as that for patients with ischemic heart disease in general. This is important because some of these patients may have abnormal left ventricular function or less than complete revascularization and because some grafts may have occluded. Adequate preoperative medication, careful intraoperative and postoperative monitoring, smooth induction of anesthesia with avoidance of hypertension as well as hypotension and avoidance of myocardial depressing agents are all very important. Continuous monitoring of

blood pressure using an indwelling intraarterial catheter is recommended in all patients. In patients with a clinical history of congestive heart failure or with evidence of earlier left ventricular dysfunction, the preoperative insertion of a Swan-Ganz catheter for the monitoring of pulmonary artery wedge pressure is also very beneficial. This is also helpful even in patients with normal left ventricles if it is anticipated that the thoracic or abdominal aorta has to be clamped temporarily. In these cases, if the blood pressure or the pulmonary artery wedge pressure rises during temporary occlusion of the aorta, vasodilator therapy using nitroprusside or other appropriate agents should be initiated to decrease the risk of intraoperative imbalance of oxygen supply and demand. In cases in which the need of inotropic support arises during or after operation (decreased cardiac output with adequate filling pressure) the agent that results in the least increase in oxygen demand should be used. Our present drug of choice in these cases in dobutamine hydrochloride because of its low arrhythmogenic and chronotropic effect.

We conclude that coronary revascularization provides significant protection against cardiac complications in patients with ischemic heart disease undergoing noncardiac operations.

REFERENCES

1. Steen PA, Tinker JH, Tarhan S: Myocardial reinfarction after anesthesia and surgery. JAMA 239:2566-2570, Jun 1980

2. Debakey ME, Crawford ES, Cooley DA, et al: Aneurysm of abdominal aorta analysis of results of graft replacement therapy one to eleven years after operation. Ann Surg 160:622-639, Oct 1964

3. Thompson JE, Hollier LH, Patman RD, et al: Surgical management of abdominal aortic aneurysm: Factors influencing mortality and morbidity—A 20 year experience. Ann Surg 181:654-661, May 1975

4. Young AE, Sandberg GW, Couch NP: The reduction of mortality of abdominal aortic aneurysm resection. Am J Surg 134:585-590, Nov 1977

5. Hertzer NR: Fatal myocardial infarction following abdominal aortic aneurysm resection—343 patients followed 6 to 11 years postoperatively. Ann Surg 192:667-673, Nov 1980

6. Hertzer NR, Loop FD, Taylor PC, et al: Staged and combined surgical approach to simultaneous carotid and coronary vascular disease. Surgery 84:803-811, Dec 1978

7. Mahar LJ, Steen PA, Tinker JH, et al: Peri-operative myocardial infarction in patients with coronary artery disease with and without aortocoronary artery bypass grafts. J Thorac Cardiovasc Surg 76:533-537, Oct 1978

8. Crawford ES, Morris GC, Howell JF, et al: Operative risk in patients with previous coronary artery bypass. Ann Thorac Surg 26:215-221, Sep 1978

9. Ennix CL, Lawrie GM, Morris GC, et al: Improved results of carotid endarterectomy in patients with symptomatic coronary disease: An analysis of 1,546 consecutive carotid operations. Stroke 10:122-125, Mar-Apr 1979

10. Hertzer NR, Young JR, Kramer JR, et al: Routine coronary angiography prior to elective aortic reconstruction—Results of selective myocardial revascularization in patients with peripheral vascular disease. Arch Surg 114:1336-1344, Nov 1979

11. Mehigan T, Buch WS, Pipkin RD, et al: Planned approach to coexistent cerebrovascular disease in coronary artery bypass candidates. Arch Surg 112:1403-1409, Nov 1977

12. Thompson JE, Austin DJ, Patman RD: Carotid endarterectomy for cerebrovascular insufficiency—Long-term results in 592 patients followed up to 13 years. Ann Surg 172:663-679, Oct 1970

13. Gage AA, Bhayana JN, Balu V, et al: Assessment of cardiac risk in surgical patients. Arch Surg 112:1488-1492, Dec 1977

14. Cutler BS, in discussion, Hertzer NR, Young JR, Kramer JR, et al: Routine coronary angiography prior to elective aortic reconstruction—Results of selective myocardial revascularization in patients with peripheral disease. Arch Surg 114:1336-1344, Nov 1979

Refer to: Saiki J, Vaziri ND, Barton C: Perinephric and intranephric abscesses: A review of the literature. West J Med 136:95-102, Feb 1982

Perinephric and Intranephric Abscesses: A Review of the Literature

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Perinephric and intranephric (renal cortical and corticomedullary) abscesses, which may coexist, are associated with considerable mortality (21 percent to 56 percent) and are often difficult to diagnose. Most cases of renal cortical abscess are due to hematogenous seeding from distant foci of infection (often involving Staphylococcus aureus*), while corticomedullary and perinephric abscesses are most often due to complications of urinary tract infections. Newer noninvasive studies such as ultrasonography, computerized tomography, gallium scanning and indium-labeled leukocyte scanning may facilitate determination of the diagnosis. While antibiotic therapy alone may suffice for the treatment of cortical abscesses, surgical drainage is an added requirement for the treatment of perinephric abscess.*

PERINEPHRIC AND INTRANEPHRIC abscesses refer to suppuration in the perirenal fascia and the renal parenchyma (cortical or corticomedullary areas) respectively. These processes may coexist and frequently are difficult diagnostic problems, with as many as 25 percent to 30 percent of cases identified only at autopsy.[1-3] Since their first description, the origin, symptomatology and clinical course of perinephric and intranephric abscesses have been substantially altered by the introduction of newer antibiotic therapy. With the development of ultrasonography, computerized tomography (CT) and radionuclide scanning techniques (gallium 67 and indium 111) as diagnostic modalities, earlier diagnosis and lower mortality might be possible.

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Epidemiology

More than 500 cases of perinephric and intranephric abscesses have been reported since they were first described. In 1474, Colot incised and drained what may have been a perinephric abscess, with an apparent complete recovery.[4] Subsequently, Hevin described the association of flank abscesses with the perinephric space and renal stones;[4,5] and, finally, the description of renal carbuncle has been credited to Israel.[6-12]

The reported incidence of perinephric and intranephric abscesses ranges from fewer than 1.3 to as many as 10 cases per 10,000 hospital admissions.[1,4,13] In the preantibiotic era, 80 percent of the cases were due to hematogenous seeding from distant foci of infection,[14-16] predominantly young adults were affected, men were affected more often than women, the right side was involved more frequently than the left and an antecedent history of renal disease was often lacking.[6,15-17] According

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
CT = computerized tomography

TABLE 1.—*Predisposing Factors to Renal Parenchymal Abscess*

Furuncles and carbuncles of skin
Dental abscesses
Pulmonary abscesses
Osteomyelitis
Renal calculi
Obstructive uropathy
Calculi
No calculi
Stricture of ureters
Neoplasm
Neurogenic bladder
Ureterovesical reflux
Mechanical bladder outlet obstruction
Papillary necrosis
Genitourinary tuberculosis
Trauma
Polycystic kidney disease
Diabetes mellitus
Glucocorticoid therapy
Intravenous drug abuse

to recent reports, however, most cases occur due to complications of urinary tract infections,[18,19] men and women are affected with equal frequency, the right and left sides are equally involved, the incidence increases with age and an abnormality of the genitourinary system often exists.[1,3,5,19-25]

As has been noted, perinephric and intranephric abscesses may coexist. One of the routes of progression of intranephric abscesses is by perforation through the renal capsule to the perinephric space. According to several authors, this process is the cause of perinephric abscess in 60 percent to 90 percent of the cases.[3,5,20]

Intranephric (Renal Parenchymal) Abscesses

Pathogenesis and Etiology

Several conditions are known to predispose to the development of renal parenchymal abscesses (Table 1). Abscesses of the skin, oral cavity, lung or bone may result in bacteremia and metastasis of infection to the renal parenchyma. Renal calculi may harbor infection and cause localized obstruction.[6,18,23] Urinary tract obstruction is generally considered a predisposing factor to urinary tract infection. However, according to Freedman,[26] uncomplicated urinary tract obstruction above the bladder is rarely associated with spontaneous infection; moreover, according to Wright and Howards[27] most patients with intravesical obstruction remain uninfected in the absence of instrumentation. In the presence of bacteria the obstructed kidney is more susceptible to infection,[28] and instrumentation during diagnostic or therapeutic procedures may play a major role in introducing pathogenic bacteria.

Genitourinary tuberculosis, which can cause strictures and deformities in the renal parenchyma and throughout the urinary tract, may also predispose to renal abscesses. Various types of trauma, including renal biopsy, can lead to abscess formation due to infection of the resulting hematoma.[3] Infected cysts in patients with polycystic kidney disease may metamorphose into abscesses.[28] Diabetic patients are thought to be susceptible to various complications of urinary tract infection. According to several authors, the incidence of renal abscesses in persons with diabetes is twice that in nondiabetic persons.[24,26,30] Glucocorticoid therapy by its known immunosuppressive effect and intravenous drug abuse through the use of contaminated needles and drug preparations have also been considered predisposing conditions.[1,8,31-33] The latter may be due to direct inoculation of bacteria into the blood stream, skin abscesses, phlebitis or bacterial endocarditis.

Anatomically, renal parenchymal abscesses may be divided into cortical and corticomedullary abscesses. Gelman and Stone[8] have postulated that hematogenous spread of infection tends to favor cortical involvement because of its ample blood and lymphatic supply. The hypertonicity of the medullary region, on the other hand, tends to impair leukocyte function and to favor the survival of cell wall-deficient forms of bacteria. No conclusive evidence yet exists, however, to suggest involvement of cell wall-deficient bacteria in such infections, though it remains a theoretic possibility. In addition, the high ammonia content of the renal medulla can impair the defense mechanism by inactivating the fourth component of the complement system. Despite their distinct anatomic and physiologic differences, differentiation of the abscesses in the two regions is of limited clinical value because prediction of infecting organisms is not always possible,[5,34] and therapy is not necessarily different.[35-41]

Regardless of their site and origin, renal parenchymal abscesses may evolve in one or more of

the following ways: perforation of the renal capsule and formation of a perinephric abscess, extension toward the renal pelvis and drainage into the collecting system or development into a chronic abscess.[8,37,42-44] The therapeutic approach differs when the abscess perforates through the renal capsule.

In the 1960's parenchymal abscesses were due predominantly to *Staphylococcus aureus* (95 percent of cases).[9,41] In recent years, however, Gram-negative bacteria have predominated and account for 50 percent to 60 percent of reported cases.[7,17,22,33,41]

Clinical Presentation

Common complaints include elevated temperature and flank or abdominal pain. Fever is present 50 percent to 100 percent of the time and flank or abdominal pain is noted in 20 percent to 86 percent of the patients.[6,22,33,41] Dysuria is present in only 14 percent to 40 percent of the reported cases.[22,41]

Leukocytosis, though common, is usually moderate and leukocyte counts are frequently less than 15,000 per cu mm.[33] The urinalysis is often abnormal, with pyuria, bacteriuria or both reported in over 70 percent of cases.[33,41] However, a normal urinalysis does not exclude the diagnosis.[11]

In general, the clinical and laboratory findings may or may not point to the urinary tract as the focus of infection and, additionally, may not distinguish renal abscess from other urinary tract infections such as pyelonephritis.

Radiologic Features

Radiologic features may be important in the investigation of renal parenchymal lesions. The features, however, may be nonspecific depending on the location of the lesion, its pathologic nature and associated conditions.[32,45,46]

With excretory urography, the acute abscess usually shows a variable degree of decreased opacification of the entire kidney or a portion thereof. A single large abscess may be seen as a bulge in the outline of the kidney or distortion of the calyces. Calyceal destruction and cavitation may suggest extension of the abscess to the collecting system. With tomography the abscess appears as a poorly demarcated lucent defect. The findings may simulate those of a benign cyst; however, in contrast to cysts the margins are not well-defined and the walls are thick. Subacute and chronic abscesses have thicker walls and irregular contours and may be difficult to distinguish from a neoplasm with central necrosis.[45]

An intrarenal abscess may be successfully identified by angiography, especially when conventional radiographic procedures are nondiagnostic.[47] Both selective and lumbar arteriography may be useful in defining the anatomic extent of the abscess.[45] Angiographic features of acute abscess differ from those of chronic abscesses.[48] In acute abscess, the major findings include displacement of vessels about a mass,[32,44,45,49] diminished radiolucency on nephrogram and loss of the usually sharp renal margin and the corticomedullary junction. A slowed blood flow through the small renal vessels adjacent to the abscess and a slightly increased blush at the margin of the lesion may be noted, but no abnormal tumor vessels exist.[32,45,47] The capillary phase usually reveals an avascular radiolucent defect with shaggy borders.

The angiographic appearance of a chronic abscess may be identical to that of a poorly vascularized renal cell carcinoma.[32,45,50-54] Due to the long-standing inflammation, the lesion may have a thick wall and increased vascularity along its margins. A large number of abnormal vessels with irregular configuration supplying the chronic inflammatory mass may be seen, which may be difficult to distinguish from tumor vessels.[45,55,56] A dense blush during the capillary-nephrogram phase and early venous filling may be observed.[52]

It has been postulated that administration of epinephrine can constrict the vessels of an abscess but may not affect abnormal tumor vessels. The reliability of this test has been debated, however, because it may not reliably distinguish a chronic abscess from a hypovascular neoplasm.

With pelvicalyceal involvement, kidneys are often nonfunctional and contain multiple stones.[57,58] In such cases, the pelvicalyceal system is often obstructed, exhibiting angiographic findings of hydronephrosis and hypervascularity of the affected calyces, which are usually distended and have ill-defined borders.

Computerized tomography (CT) is also used to investigate suspected renal parenchymal abscess. CT can demonstrate intrarenal collections of fluid and gas and define the anatomic extent of the disease.[59] Due to its noninvasive nature, and with its increasing availability and refinement, CT may eventually supplant the more invasive procedures.

Ultrasonography has proved useful in the detec-

tion and localization of renal abscesses.[18,37,38,60-64] Moreover, percutaneous aspiration of these abscesses for diagnostic and therapeutic purposes can be done using this technique[60,65,66] and the effect of therapy can be monitored by serial examinations.[38,60] Based on the surgical and postmortem findings, the accuracy of ultrasonography in the diagnosis of renal abscess is about 75 percent to 92 percent.[62,66] Ultrasonography appears to be a relatively accurate, noninvasive diagnostic tool in this situation.

Radioisotope scanning offers another noninvasive technique for the evaluation of possible renal abscess. Gallium 67 has been used in the detection of renal parenchymal abscesses.[67-72] Hopkins and co-workers[70] reported on the usefulness of this procedure in four patients, two of whom had nondiagnostic radiologic and ultrasonographic studies. However, in a large series of patients with suspected acute pyelonephritis, the test was associated with 15 percent false-positive and 13 percent false-negative results.[69] Abnormal renal uptake of gallium citrate Ga 67 may also occur with neoplastic infiltration, vasculitis, acute tubular necrosis or renal failure due to other causes, suggesting nonspecificity of this procedure.[69] Gallium citrate Ga 67 also accumulates nonspecifically in the colon.[73]

Use of radioisotope scanning with leukocytes tagged with indium 111 has the advantage of rapid accumulation in the site of infection without nonspecific accumulation in the bowel.[73-78] However, data on its use in the detection of renal abscess are limited and its diagnostic accuracy has not yet been established.

Differential diagnostic considerations include (1) acute pyelonephritis, because both may cause fever, flank pain and abnormal findings on urinalysis. The distinction may be based on clinical response to antibiotic therapy, with defervescence and diminution of symptoms generally occurring in 48 to 72 hours with pyelonephritis. (2) Chronic abscesses and hypovascular renal cell carcinoma may occasionally be clinically and radiologically indistinguishable, requiring surgical exploration for definitive diagnosis. (3) Occasionally, a renal abscess may present as a fever of unknown origin.

Treatment

Surgical drainage and debridement (possibly nephrectomy) have been the accepted treatment, though there are multiple reports of resolution with antibiotic therapy alone.[35-37,39,63,64,70,79] Most abscesses responding to nonsurgical management have been caused by *S aureus*[35,36] though some cases of Gram-negative abscesses confined to the renal parenchyma have also cleared without surgical drainage.

Appropriate parenteral antibiotic therapy for a minimum of ten days, followed by oral antibiotic therapy for an additional two to four weeks, has been associated with clinical and radiologic recovery.[35,80] *S aureus* and Gram-negative enteric organisms (such as *Escherichia coli, Klebsiella* and *Proteus*) are the most common infecting organisms.[7,9,17,22,33,41] For staphylococcal abscesses, oxacillin sodium in a dosage of 4 to 12 grams per day given intravenously has been reported to result in gradual defervescence over five to six days and abatement of symptoms in seven patients.[35] One patient received gentamicin sulfate, 240 mg daily, and another ampicillin sodium, 6 grams daily, in addition to the oxacillin in this series. After a minimum of ten days, oral penicillinase-resistant antibiotics were administered for an additional two to four weeks. Dicloxacillin sodium, 2 grams daily, was the antibiotic in these cases.

With enteric Gram-negative organisms, antibiotic selection includes aminoglycosides, cephalosporins, ampicillin, tetracycline hydrochloride and sulfa drugs.[41] Klein and Filpi[40] report that in one of their cases the abscess resolved with antibiotics but the type, dosage and duration of therapy were not described. It seems reasonable to continue with parenteral administration of appropriate antibiotics until the resolution of fever or clinical improvement are attained. Oral antibiotic therapy can then be instituted for a total of four to six weeks.

Use of percutaneous aspiration as a successful diagnostic and therapeutic tool combined with systemic antibiotic therapy has been reported in five patients.[65] In one of these cases, the abscess had failed to completely resolve with antibiotics alone. Percutaneous aspiration can be of considerable value when combined with careful clinical and microbiologic studies.

Perinephric Abscess

Pathogenesis and Etiology

Perinephric abscess arises from rupture of an intrarenal abscess into the perinephric space in 60 percent to 90 percent of the cases.[3,5,20] Other causes include inoculation of the area by way of

the bloodstream or regional lymphatics (up to 30 percent of cases)[5,15] and spread of infection from adjacent disorders such as diverticulitis; appendicitis; perforated carcinoma of the colon; inflammatory lesions of the liver, gallbladder, pancreas, pleura or pelvic structures (prostatitis, prostatic abscess, infections of the female reproductive system), and osteomyelitis of adjacent ribs or vertebrae.[1,81-83]

Conditions known to predispose to the development of perinephric abscesses are essentially similar to those of renal parenchymal abscesses (Table 1) with the addition of the above adjacent foci of infection.

From the perinephric area, the infection can spread in several ways as governed by the anatomy of Gerota's fascia.[4] An abscess in the perinephric space may penetrate into the flank muscles or into the psoas muscle; it may extend caudally between the diverging layers of Gerota's fascia and present as an abscess in the groin or paravesical area. Less commonly, there may be extension into the peritoneal cavity. Cephalad extension may lead to formation of a subphrenic abscess, penetration of the diaphragm and empyema formation, lung abscess, or nephrobronchial fistula.[79,84,85] Rupture into the colon occurs infrequently.

Pathogenic bacteria found in five different series are listed in Table 2.[3,18,19,23,33] Not all abscesses were bacteriologically studied; 27 percent of patients in Salvatierra and associates' review[19] and 37 percent of patients in the series by Thorley and co-workers[3] did not have cultures. Occasionally abscesses may appear to be "sterile," suggesting prior antibiotic therapy or infection with more fastidious organisms (anaerobes, fungi and the like). Blood cultures are frequently positive in perinephric abscess,[3] but notably *S aureus* may be present in the blood and urine without discernible renal parenchymal or perirenal involvement.[25] While organisms isolated from urine frequently correlate with those isolated from the abscess, Malgieri and co-workers[18] and Atcheson[17] have found different organisms on cultures of urine and abscess material in 30 percent to 60 percent of their cases.

Clinical Presentation

A summary of the presenting symptoms and physical findings compiled from three recent reviews is shown in Table 3.[3,19,23]

The most common presenting complaints are fever (in about 90 percent of cases) and pain (in about 70 percent to 80 percent of cases). Temperature elevation may be mild (between 38-39°C

TABLE 2.—*Etiologic Organisms of Perinephric Abscesses*

	Positive Cultures	
	Number	Percent
Salvatierra and co-workers, 1967[19] (71 patients—52 abscess cultures, 14 with more than one organism)		
Staphylococcus aureus plus other organism	10	
Gram-negative organisms	55	
Proteus sp	22	
Escherichia coli	19	
Pseudomonas	6	
Aerobacter aerogenes	3	
Klebsiella	3	
Paracolobactrum	2	
Sterile	4	
Thorley and co-workers, 1974[3] (52 patients—43 causative organisms identified)		
S aureus	6	
E coli	16	
Proteus sp	6	
Paracolobactrum	3	
Enterobacter	2	
Pseudomonas	2	
Klebsiella	2	
Streptococcus viridans	1	
Serratia	1	
Citrobacter	1	
Sterile (probably anaerobes)	1	
Abscess culture not done, multiple urinary pathogens	2	
Malgieri and co-workers, 1977[18] (27 of 43 reported patients had perinephric abscess, 90 percent had urine cultures, 70 percent of abscess cultures correlated with urine cultures)		
S aureus	3	
Urine cultures		
E coli		43
Proteus		29
Pseudomonas	9	
Aerobacter	6	
Sterile	13	
Truesdale and co-workers, 1977[23] (26 patients—22 had positive cultures, 2 had more than one organism)		
Staphylococcus aureus	5	
Staphylococcus epidermidis	1	
Hemolytic *Streptococcus*	1	
Nonhemolytic *Streptococcus*	1	
Proteus	11	
E coli	2	
Pseudomonas	2	
Klebsiella	1	
No growth	4	
Anderson and McAninch, 1980[33] (23 cases of perinephric abscess)		
S aureus	2	9
E coli	9	39
Proteus	2	9
Pseudomonas	3	10
More than one organism	9	

TABLE 3.—*Clinical Features of Perinephric Abscess*

Symptoms	Number of Patients Affected	Total	Percentage
Elevated temperature	133	149	89
Pain—flank	63	78	80
abdominal	31	52	60
unspecified	51	71	72
Chills	52	123	42
Dysuria	48	123	39
Nausea, vomiting	16	71	23
Weight loss	24	97	25
Weakness	10	71	14
Moribund	7	71	10
Signs			
Flank tenderness	38	52	73
Abdominal tenderness	33	52	63
Temperature >100	73	123	59
>102	14	123	11
Mass—flank	58	123	47
abdomen	18	52	35

[100-102°F]) in about 10 percent, and absent or low grade in 30 percent. The pain is often localized to the flank or abdomen and may be referred to the inguinal area, genitalia, hip, thigh or knee. Chills and dysuria are present in about 40 percent of patients, and weight loss, nausea and vomiting in 25 percent. Physical findings include flank tenderness in about 75 percent and abdominal tenderness in about 60 percent of the cases. A flank mass or abdominal mass may be present in 47 percent and 35 percent of the cases respectively. Additionally, scoliosis with splinting on the affected side and pain on bending toward the contralateral side is present in some patients.[86]

The presentation of perinephric abscess may be insidious. In two series where data on duration of symptoms were given, 58 percent of 135 patients had symptoms for longer than 14 days.[3,16] In a third series, a "significant number" of patients had symptoms ranging from one to four weeks.[19]

As with renal parenchymal abscesses, routine laboratory tests are not particularly helpful in establishing the diagnosis of perinephric abscess.[5,9] Although the leukocyte count is often elevated, the elevation tends to be mild, with fewer than 13,000 leukocytes per cu mm in 40 percent of patients in a recent study.[3] Anemia with hemoglobin concentrations under 10 grams per dl is found in about 40 percent[1,3-5] and significant azotemia (blood urea nitrogen [BUN] greater than 50 mg per dl) is found in about 25 percent of the cases.[5] Interestingly, urinalysis may have entirely normal findings in 25 percent to 30 percent of cases.[1,3,5,11]

Radiologic Findings

When present, unilateral abnormalities on supine abdominal film, roentgenogram of the chest and excretory urogram are helpful in the diagnosis of perinephric abscess. Supine abdominal film may reveal absent psoas shadows, upper quadrant mass, absent renal shadow, urinary stone or retroperitoneal gas.[3] Roentgenogram of the chest may reveal pleural effusions, lower lobe infiltrates or elevated hemidiaphragm. Upper lobe infiltrate and apical scarring have also been mentioned,[3] but no satisfactory explanation has been offered regarding the mechanism of the latter findings. The possible abnormalities on excretory urography include absent or diminished function, caliectasis, calyceal stretching, stones, displacement of the renal shadow (usually medially and upward) and displacement or abnormalities of the overlying bowel.[3,87] Abnormalities were found on 42 percent of supine abdominal films, 42 percent of chest x-ray films and 75 percent of the excretory urograms in one series.[7] The authors noted that when all three studies were done, a unilateral abnormality was found in at least one of the studies in 90 percent of the cases.

Additionally, assessment of renal mobility with respiration or position may be quite useful.[3,5,13,86,88,89] Mobility may be assessed by abdominal fluoroscopy, plain films of the abdomen during inspiration and expiration or by supine and upright abdominal films with or without administration of contrast media. A normal kidney moves between 2 and 6 cm with respiration and positional changes.[13,88] Perirenal inflammation decreases renal mobility in up to 90 percent of cases.

Retrograde pyelography is useful in evaluating obstructive lesions distal to the pelvis as a cause of poor functioning or nonfunctioning of a kidney. In a recent study, retrograde pyelograms were found to have abnormal findings in 35 percent of the patients with proved perinephric abscess.[5] Abnormalities included calyceal stretching, stone and extravasation of contrast material. The latter may also be seen on excretory urography and, though uncommon, is virtually diagnostic of perinephric abscess.[1,4,13,45,60,90]

With angiography, perinephric abscess usually causes abnormalities of the renal margin.[57,58] Characteristic findings include increased number and size of the perforating arteries extending from

the kidney, stretching and prominence of tortuous capsular and perhaps pelvic arteries around the abscess and a contrast blush.

As with renal parenchymal abscess, computerized tomography is helpful in the diagnosis of perinephric abscess and delineation of the extent and route of its propagation with excellent detail.[59] This information is of great importance in planning the surgical drainage of the abscess.

Radionuclide scanning with gallium citrate Ga 67 or indium In 111, while often revealing renal or perirenal inflammation, provides insufficient detail to allow distinction of pyelonephritis from renal parenchymal and perinephric abscesses.[59,69] Other lesions such as renal neoplasms and acute tubular necrosis may also be gallium-avid.[69]

Diagnosis

Despite the apparent prevalence of signs and symptoms referable to the kidney and urinary tract, prompt and accurate diagnosis of perinephric abscess has not been achieved satisfactorily. The correct diagnosis on admission was noted in 18 percent of 71 patients reported by Salvatierra and co-workers[19] and 35 percent of the patients reported by Thorley and colleagues.[3] In an earlier review by Atcheson,[17] the diagnosis was delayed in 49 percent of the patients. The diagnosis is made on postmortem examination only in 25 percent to 30 percent of the patients.[1-3]

Differential diagnostic considerations are similar to those entertained with renal parenchymal abscess. Acute uncomplicated pyelonephritis is generally distinguished by an earlier presentation and a more rapid response to therapy. Perinephric abscess should be considered in the event of a fever of unknown origin and in cases of suppurative foci such as empyema, pelvic abscess and peritonitis where clear explanation for such infections is lacking.

Prognosis

According to several reports mortality ranges from 21 percent to 56 percent.[3,15,18,19] The prognosis is generally better with surgical incision and drainage, but even then the reported mortality is as high as 25 percent.

Treatment

Surgical drainage remains the standard treatment. When the abscess involves the perinephric space, antibiotic therapy alone is not likely to be curative.[12,34] Antibiotics should thus be considered as an adjunct in the treatment of perinephric abscesses.[33,40,41] The optimal duration of antibiotic therapy, however, has not been established by controlled studies.[91] Percutaneous aspiration is potentially useful in draining the perinephric abscess, although current reports involve its use only for renal parenchymal abscesses.[61,65]

Conclusion

Perinephric abscess and renal carbuncle may present as different diagnostic and therapeutic problems. In the past, the diagnosis of these entities was often delayed and mortality was quite high, even with appropriate therapy. With the availability of noninvasive, accurate diagnostic modalities, such as ultrasonography, radionuclide scanning and computerized tomography, considerable improvement in the diagnosis and management of perinephric and renal parenchymal abscesses might be expected.

REFERENCES

1. Finegold SM: Perinephric abscess, *In* Hoeprich P (Ed): Infectious Diseases, 2nd Ed. Hagerstown, MD, Harper and Row, 1977, pp 474-478

2. Stevenson EOS, Ozeran RS: Retroperitoneal space abscesses. Surg Gynecol Obstet 128:1202-1208, 1969

3. Thorley JD, Jones SR, Sanford JP: Perinephric abscess. Medicine (Baltimore) 53:441-451, 1974

4. Hotchkiss RS: Perinephric abscess. Am J Surg 85:471-483, 1953

5. Sanford JP: Perinephric abscess, *In* Harrison JH, et al (Eds): Campbell's Urology, 4th Ed. Philadelphia, WB Saunders, 1978, pp 708-712

6. Doolittle KH, Taylor JN: Renal abscess in the differential diagnosis of mass in kidney. J Urol 89:649-651, 1963

7. Fair WR, Higgins MH: Renal abscess. J Urol 104:179-183, 1970

8. Gelman MI, Stone LB: Renal carbuncle: Early diagnosis by retroperitoneal ultrasound. Urology 7:103-107, 1976

9. Graves RC, Parkins LE: Carbuncle of the kidney. J Urol 35:1-14, 1936

10. Ingrish GA: Carbuncle of the kidney. J Urol 42:326-340, 1939

11. McNulty PH: Carbuncle of the kidney. J Urol 35:15-20, 1936

12. Pearlman SJ: Carbuncle of the kidney. J Urol 65:754, 1951

13. Parks RE: The radiographic diagnosis of perinephric abscess. J Urol 64:555-563, 1950

14. Laval KU, Lutzeyer W: Paranephric abscess: A changing concept. Eur Urol 5:81-85, 1979

15. Campbell MF: Perinephritis abscess. Surg Obstet Gynecol 51:674-682, 1930

16. Moore CA, Gangai MP: Renal cortical abscess. J Urol 98: 303-306, 1967

17. Atcheson DW: Perinephric abscess with a review of 117 cases. J Urol 46:201-208, 1941

18. Malgieri JJ, Kursh ED, Persky L: The changing clinicopathological pattern of abscesses in or adjacent to the kidney. J Urol 118:230-232, Aug 1977

19. Salvatierra O Jr, Bucklew WB, Morrow JW: Perinephric abscess: A report of 71 cases. J Urol 98:296-302, Sep 1967

20. Papper S: Interstitial nephritis: Perinephric abscess, Clinical Nephrology, 2nd Ed. Boston, Little, Brown, 1978, pp 273-274

21. Petersdorf RG: Localized infections and abscesses: Renal abscess, *In* Thorn GW, et al (Eds): Harrison's Principles of Internal Medicine, 8th Ed. New York, McGraw-Hill, 1976, pp 790-797

22. Timmons JW, Permutter AD: Renal abscess: A changing concept. J Urol 115:299-301, Mar 1976

23. Truesdale BH, Rous SN, Nelson RP: Perinephric abscess: A review of 26 cases. J Urol 118:910-911, 1977

24. Plevin SN, Balodimos MC, Bradley RF: Perinephric abscess in diabetic patients. J Urol 103:539-543, 1970

25. Lee BK, Crossley K, Gerding DN: The association between *Staphylococcus aureus* bacteremia and bacteriuria. Am J Med 65:303-306, Aug 1978

26. Freedman LR: Interstitial renal inflammation, including pyelonephritis and urinary tract infection, *In* Earley LE, Gottschalk CW (Eds): Strauss and Welt's Diseases of the Kidney, Vol 2, 3rd Ed. Boston, Little, Brown, 1979, pp 817-876

27. Wright FS, Howards SS: Chap 38, *In* Brenner BM, Rector FC (Eds): The Kidney, Vol 2, 2nd Ed. Philadelphia, WB Saunders, 1981, pp 2008-2044

28. Beck LH, Stein JH, Earley LE: Chap 20 *In* Earley LE, Gottschalk CW (Eds): Diseases of the Kidney, Vol 2, 3rd Ed. Boston, Little, Brown, 1979, pp 877-892

29. Sweet R, Keane WF: Perinephric abscess in patients with polycystic kidney disease undergoing chronic hemodialysis. Nephron 23:237-240, 1979

30. Simpkins KC, Barraclough NC: Renal cortical abscess, perinephritis and perinephric abscess in diabetes. Br J Radiol 46: 433-436, 1973

31. Renal carbuncle (Editorial). Br Med J 3:63, 1973

32. Caplan LH, Siegelman SS, Bosniak MA: Angiography in inflammatory space-occupying lesions in the kidney. Radiology 88:14-23, 1967

33. Anderson KA, McAninch JW: Renal abscesses: Classification and review of 40 cases. Urology 16:333-338, 1980

34. Khashu BL, Seery WH, Rothfeld SH: Nonstaphylococcal bacteria in renal cortical abscess. Urology 7:256-259, 1976

35. Schiff M, Glickman M, Weiss, et al: Antibiotic treatment of renal carbuncle. Ann Intern Med 87:305-308, 1977

36. Lyons RW, Long JM, Lytton B, et al: Arteriography and antibiotic therapy of a renal carbuncle. J Urol 107:524-526, 1972

37. Schneider M, Becker JA, Staiano S, et al: Sonographic correlation of renal and perirenal infections. Am J Roentgenol 127:1007-1014, 1976

38. Conrad MR, Sanders RC, Mascardo AD: Perinephric abscess aspiration using ultrasound guidance. Am J Roentgenol 128:459-464, 1977

39. Longo VJ: Management of renal carbuncle (Letter). J Urol 120:124, 1978

40. Klein DL, Filpi RG: Acute renal carbuncle. J Urol 118: 912-915, 1977

41. Hoverman IV, Gentry LO, Jones DW, et al: Intrarenal abscess: Report of 14 cases. Arch Intern Med 140:914-916, 1980

42. Colby FH, Baker MP, St Goar WT: Renal carbuncle: Report of a response to modern treatment. N Engl J Med 256:1147-1148, 1957

43. Rose TF: Renal carbuncle: A report of five cases, with some remarks on aetiology and treatment. Med J Aust 2:58-62, 1953

44. Rabinowitz JG, Kinkhabwala MN, Robinson T, et al: Acute renal carbuncle. Am J Roentgenol 116:740-748, 1972

45. Evans JA, Meyers MA, Bosniak MA: Acute renal and perirenal infections. Semin Roentgenol 6:276-291, Jul 1971

46. Welch NM, Prather GC: Renal carbuncle (staphylococcal abscess of the kidney). J Urol 62:646-650, 1949

47. Gilbert PG, Shirley SW: The use of angiography in the diagnosis of space-occupying renal perirenal inflammatory lesions. J Urol 110:11-15, 1973

48. Craven JD, Hardy B, Stanley P, et al: Acute renal carbuncle: The importance of preoperative angiography. J Urol 111: 727-731, Jun 1974

49. Himmelfarb EH, Rabinowitz JG, Kinkhabwala MN, et al: The roentgen features of renal carbuncle. J Urol 108:846-851, Dec 1972

50. Becker JA, Fleming R, Kanter I, et al: Misleading appearances in renal angiography. Radiology 88:691-700, 1967

51. Caro G, Meisell R, Held B: Epinephrine-enhanced arteriography in renal and perirenal abscess—A differential diagnostic problem. Radiology 92:1262-1264, May 1969

52. Combs JA, Crummy AB, Crossman FP: Angiography in renal and pararenal inflammatory lesions—The significance of early venous filling. Radiology 98:401-403, Feb 1971

53. Kahn PC, Wise HM Jr: Simulation of renal tumor response to epinephrine by inflammatory disease. Radiology 89:1062-1064, 1967

54. Salmon RB, Koehler PR: Angiography in renal and perirenal inflammatory masses. Radiology 88:9-13, 1967

55. Fenlon JW, Silber I, Koehler PR: Perirenal masses simulating renal tumors. J Urol 106:448-450, Oct 1971

56. Levin DC, Gordon D, Kinkhabwala M, et al: Reticular neovascularity in malignant and inflammatory renal masses. Radiology 120:61-68, 1976

57. Koehler PR: The roentgen diagnosis of renal inflammatory masses—special emphasis on angiographic changes. Radiology 112: 257-266, Aug 1974

58. Koehler PR, Nelson JA: Arteriographic findings in inflammatory mass lesions of the kidney. Radiol Clin North Am 14:281-293, 1976

59. Mendez G, Isikoff MB, Morillo G: The role of computed tomography in the diagnosis of renal and perirenal abscesses. J Urol 122:582-586, 1979

60. Smith EH, Bartrum RJ Jr: Ultrasonically guided percutaneous aspiration of abscesses. Am J Roentgenol Radium Ther Nucl Med 122:308-312, Oct 1974

61. Renal carbuncles (Editorial). Br Med J 2:1166-1167, 1978

62. Goldman SM, Minkin SD, Naraval DC, et al: Renal carbuncle: The use of ultrasound in its diagnosis and treatment. J Urol 118:525-528, 1977

63. Pedersen JF, Hancke S, Kristensen JK: Renal carbuncle: Antibiotic therapy governed by ultrasonically guided aspiration. J Urol 109:777-778, May 1973

64. Sanders RC: The place of diagnostic ultrasound in the examination of kidneys not seen on excretory urography. J Urol 114:813-821, 1975

65. Caldomone AA, Frank IN: Percutaneous aspiration in the treatment of renal abscess. J Urol 123:92-93, 1980

66. Pitts WR, Kazam E, Gershowitz M, et al: A review of 100 renal and perinephric sonograms with anatomic diagnoses. J Urol 114:21-26, 1975

67. Hampel N, Class RN, Persky L: Value of 67 gallium scintigraphy in the diagnosis of localized renal and perirenal inflammation. J Urol 124:311-314, 1980

68. Frankel RS, Richman SD, Levenson SM, et al: Renal localization of gallium-67 citrate. Radiology 114:393-397, 1975

69. Hauser MF, Alderson PO: Gallium-67 imaging in abdominal disease. Semin Nucl Med 8:251-270, 1978

70. Hopkins GB, Hall RL, Mende CW: Gallium-67 scintigraphy for the diagnosis and localization of perinephric abscesses. J Urol 115:126-128, Feb 1976

71. Raghavaiah NV: Gallium-67 scintigraphy in the diagnosis of renal cortical abscess. J Urol 120:237-238, 1978

72. Patel R, Tanaka T, Mishkin F, et al: Gallium-67 scan: Aid to diagnosis and treatment of renal and perirenal infections. Urology 16:225-228, 1980

73. Coleman RE, Black RE, Welch DM, et al: Indium-111 labeled leukocytes in the evaluation of suspected abdominal abscesses. Am J Surg 139:99-104, 1980

74. Dutcher JP, Schiffer CA, Johnston GS: Rapid migration of "indium-labeled" granulocytes to sites of infection. N Engl J Med 304:586-589, Mar 5, 1981

75. Ascher NL, Ahrenholz DH, Simmons RL, et al: Indium-111 autologous tagged leukocytes in the diagnosis of intraperitoneal sepsis. Arch Surg 114:386-392, 1979

76. Segal AW, Arnot RN, Thakur ML, et al: Indium-111-labeled leukocytes for localization of abscesses. Lancet 2:1056, 1976

77. Forstrom L, Gomez L, Weiblen B, et al: Clinical use of indium-111 oxine labeled leukocytes in the detection of inflammation or abscess (Abstract). J Nucl 19:672-673, 1978

78. Thakur ML, Coleman RE, Welch MJ: Indium-111-labeled leukocytes for the localization of abscesses: Preparation, analysis, tissue distribution, and comparison with gallium-67 citrate in dogs. J Lab Clin Med 89:217-228, Jan 1977

79. Cobb OE: Carbuncle of the kidney. Br J Urol 38:262-267, 1966

80. Rives RK, Harty JI, Amin M: Renal abscess: Emerging concepts of diagnosis and treatment. J Urol 124:446-447, Oct 1980

81. Altemeier WA, Alexander JS: Retroperitoneal abscess. Arch Surg 85:512-524, 1961

82. Falk VS: Obstructive jaundice and perinephric abscess (Letter). Arch Surg 113:778, 1978

83. Murray HW, Molavi A: Perinephric abscess: An unusual presentation of perforation of the colon. Johns Hopkins Med J 140:15-18, 1977

84. Caberwal D, Katz J, Reid R, et al: A case of nephrobronchial and colonobronchial fistula presenting as lung abscess. J Urol 117:371-373, Mar 1977

85. Neilson AM, Dick GF, Maddock WG: Chronic perinephric abscess with perinephro-bronchial fistula and psoas abscess. J Urol 63:433-437, 1950

86. Foulds GS: Diagnosis of perinephric abscess. J Urol 42:1, 1939

87. Meyers MA: Colonic changes secondary to left perinephritis: New observations. Radiology 111:525-528, 1974

88. Golden GT, Roberts TI, Donato AT: Prolonged postoperative fever caused by a perinephric abscess: Diagnosis by "Mathe's sign." Am Surg 40:302-304, 1974

89. Mathe CP: Diagnosis and treatment of perinephric abscess: Renal fixation a new roentgenographic diagnostic sign. Am J Surg 38:35-49, 1937

90. LeComte RM: Perinephritis and perirenal disease. J Urol 56:636-643, 1946

91. Gleckman RA: Perinephric abscess, *In* Gantz NM, Gleckman RA (Eds): Manual of Clinical Problems in Infectious Disease; with annotated key references. Boston, Little, Brown, 1979, pp 137-140

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Amebic Abscess of the Liver: Surgical Aspects

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During the past five years, ten documented cases of hepatic amebic abscess have required surgical intervention at Olive View Hospital, Van Nuys, California. Three of the patients underwent laparotomy when an hepatic abscess ruptured into the peritoneal cavity, and two required surgical intervention when an abscess invaded adjacent organs. Another abscess continued to enlarge despite metronidazole therapy and still another became superinfected with bacteria. In the remaining three patients, surgical procedure would have been avoided if the correct diagnosis had been made. In fact, the preoperative diagnosis in five cases was acute appendicitis. All patients survived. The incidence of Entamoeba histolytica *infestation is increasing in our community. Although most patients rapidly improve with metronidazole therapy, surgical complications do arise and diagnoses are missed. This series of cases emphasizes the need for surgeons working in Southern California to familiarize themselves with the clinical features, complications and appropriate surgical treatment of amebiasis.*

INFECTION BY THE PARASITE *Entamoeba histolytica,* known as amebiasis, can be either intestinal or extraintestinal. The intestinal type is predominant, having a wide spectrum of presentations from asymptomatic carriers to patients with amebic dysentery. It is characterized by fever, colicky abdominal pain and frequent bloody stools. In a small percentage of patients, the parasite infects other organs, typically the liver. Hepatic amebic abscesses generally give symptoms of an indolent abdominal disorder with fever, malaise, vague right upper quadrant pain and tenderness, and hepatomegaly. Radioisotopic liver scans show intrahepatic filling defects and serologic testing is positive for amebiasis in 95 percent of patients.[1] Most patients respond rapidly to amebicidal drug therapy without requiring operative intervention. On rare occasions, resistance to medical therapy necessitates a surgical procedure. An hepatic amebic abscess may also have features consistent with an acute abdominal disorder requiring operative intervention.

Olive View Hospital is a small general hospital of 143 beds located in the San Fernando Valley and serving an indigent, transient patient popula-

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tion that is mainly Spanish-speaking. In 1980 several patients with hepatic amebiasis were operated on at our hospital; that recent exposure has prompted this report, which summarizes our five-year experience with the surgical treatment of ten cases of hepatic amebiasis.

Patients and Methods

Between November 1975 and November 1980 ten patients with hepatic amebic abscess underwent operation. Seven were male and three were female; their ages ranged from 18 months to 57 years. Only five had recently traveled to a region where *E histolytica* is endemic. The ten cases were divided into three categories according to their clinical presentation: (1) preoperative diagnosis of acute appendicitis, (2) complications during medical therapy for hepatic amebiasis and (3) bacterial superinfection with consequent septicemia.

The first group operated on for acute appendicitis consisted of five patients who had abdominal pain, right lower quadrant tenderness, elevated temperature above 38.5°C (101°F) and a leukocyte count greater than 12,000 per cu mm (range 12,200 to 21,000 per cu mm). At exploration, the appendix was normal in every patient. In two cases, free pus was present in the peritoneal cavity, originating from a ruptured abscess in the right lobe of the liver. There were no other intraabdominal pathological findings. Gram stain and wet mount of a specimen of the pus showed no organisms; a presumptive diagnosis of amebiasis was made (later confirmed by serology). The peritoneal cavities of the two patients were copiously irrigated and the abscess cavities drained. Metronidazole was given postoperatively for ten days and the patients recovered. The other three patients in this first group were found at exploratory laparotomy to have only enlarged mesenteric lymph nodes. Fever and abdominal pain persisted in the postoperative period. Radionuclide liver scans (Figure 1) and serologic tests confirmed the diagnosis of hepatic abscess in each case. These patients also responded to metronidazole therapy.

Three patients made up the second group. In each of these hepatic amebiasis had been diagnosed and the appropriate therapy was started. Complications then developed in each instance that necessitated surgical intervention. Two patients failed to respond to intensive multiagent therapy and continued to have severe symptoms. In one, the abscess invaded the diaphragm and adjacent pleural cavity, creating an hepatobronchial fistula (Figure 2). The third patient became asymptomatic on metronidazole therapy,

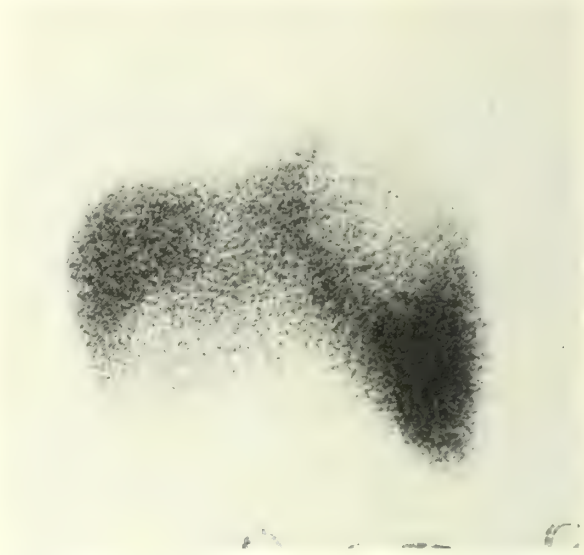

Figure 1.—Posterior view of liver scan revealing a large filling defect in the right lobe of the liver consistent with an amebic abscess.

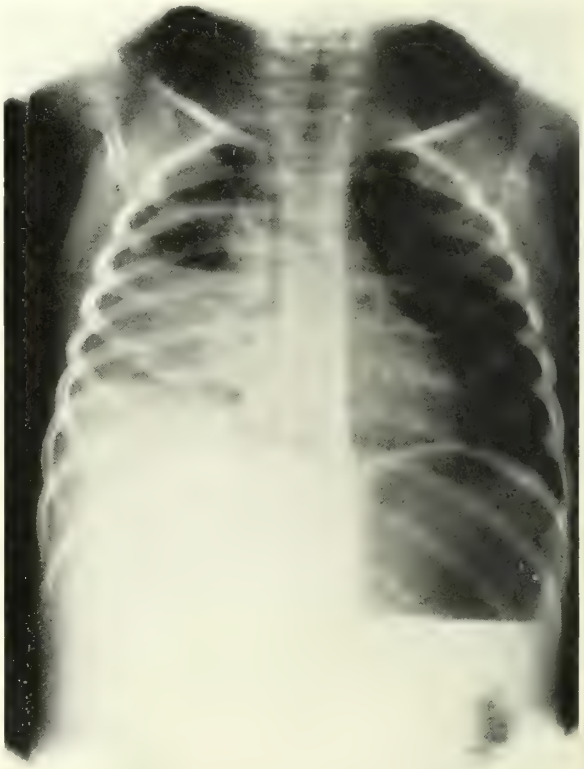

Figure 2.—Chest x-ray of a patient with an amebic liver abscess demonstrating intrathoracic extension, elevated right hemidiaphragm and an air-fluid level in the amebic empyema indicative of a communication with the bronchial tree.

but on the fifth day of treatment his abscess ruptured into the peritoneal cavity. After surgical drainage of the abscess, rapid and dramatic improvement was observed in all three patients.

The remaining two patients in this series, both of whom had hepatic amebic abscesses with bacterial superinfection, had been sick with fever and chills for more than a month. Although abdominal examination on admission was unremarkable, an extensive workup in both cases showed serology positive for amebiasis, filling defects on liver scans and polymicrobial bacteremia. At operation in one of these patients, a fistula was found between the abscess and the gallbladder. Gallstones were also present in the abscess. Contaminated bile as a consequence of cholelithiasis was the presumed source of the bacterial superinfection in this patient. In the other case, no source for the bacterial superinfection was found at laparotomy. Both patients were treated successfully with drainage of the abscess, postoperative tissue amebicides and broad-spectrum antibiotics.

Comment

Although not endemic in proportion, the prevalence of amebiasis continues to increase substantially in Southern California.[2,3] The present series of ten patients represents only the surgical cases at Olive View Hospital during a five-year period, that is, 30 percent of the patients we saw with hepatic amebiasis.

Diagnosing amebic liver abscess from clinical features can be extremely challenging. Fever (in all ten of the patients), abdominal pain (six patients) and abdominal tenderness (eight patients) were the most consistent findings. A prior illness resembling amebic dysentery had occurred in only one instance. These observations are similar to those of Adams and MacLeod[4] in their extensive series from South Africa. Travel to an endemic region could be substantiated in only five cases, but four of the remaining patients had family members who had recently arrived from Mexico. We suspect that the cysts of *E histolytica* were transmitted freely in these families.

Amebic disease masquerading as an acute abdominal emergency is not unique to our series. Other investigators have experienced the same diagnostic and therapeutic challenges.[5,6] Cognizance of the condition in an appropriate clinical setting will facilitate the correct diagnosis. Serologic tests and liver scans are the chief laboratory aids in diagnosing amebic liver abscess. Testing for the parasite in specimens of stool, from the abscess cavity or the abscess fluid, is not only difficult but seldom rewarding.[7] The indirect hemagglutination assay is a useful test and seems to be the most sensitive serologic test, though persistence of titers positive for the parasite after eradication of the clinical disease can be a problem. Several newer techniques under investigation, such as the gel diffusion precipitin test, appear promising. Radioisotope liver scans are valuable for delineating the size and location of the abscess.

Tissue amebicides are usually effective in treating amebic hepatic abscesses. The drug of choice is metronidazole (Flagyl) in a dose of 750 mg three times a day for seven to ten days.[8] In our experience, a clinical response on this regimen should occur in 48 to 72 hours. If not, the second-line drugs, chloroquine phosphate and emetine hydrochloride, should be administered. If pain, fever and tenderness persist, needle aspiration of the abscess using isotopic or ultrasonic scanning should be attempted. These techniques can be performed with few complications,[9] and in hospitals with these capabilities, blind needling of amebic abscesses is no longer necessary.

Failure of medical regimen and aspiration occurs infrequently, but when it does surgical intervention should proceed without delay. Failure to intervene appropriately at this time can increase the risk of rupture of abscess contents freely into the peritoneal cavity or into any of several contiguous organs. Other acute abdominal conditions, specifically acute appendicitis and cholecystitis, can be mimicked by amebiasis, resulting in diagnostic problems both preoperatively and postoperatively. Finally, these abscesses may infrequently become superinfected with bacteria, making drainage mandatory.

The diagnosis of amebic abscess with bacterial superinfection in two patients in this series was confirmed by positive findings on serology. It is conceivable, though, that the findings on serology represented past rather than present invasive amebiasis, and that our patients had primary pyogenic liver abscesses and not amebic abscesses. Both of these patients had a history negative for either invasive intestinal or extraintestinal amebiasis, however, and for this reason were considered to have amebic liver abscesses superinfected with bacteria.

Several large series of cases have recently been reported in the literature[10-12] in which the clinical symptomatology, diagnostic and therapeutic mo-

dalities and indications for surgical intervention are comparable to the cases reported here. Mortality has ranged from 0 to 34 percent. Our zero mortality undoubtedly reflects the good physical and nutritional status of our patients and the lack of concurrent invasive intestinal disease. These two factors contributed to the demise of those who died among the patients described in the literature.

Conclusion

In summary, a five-year experience with the surgical treatment of ten cases of hepatic amebic abscess is presented. Surgical procedures were done for complications of the disease and for diagnosis. The prevalence of the disease appears to be increasing in Southern California and it should be considered when fever and abdominal pain are present and other more obvious conditions have been ruled out. Liver scans and serologic testing facilitate the proper diagnosis and enable clinicians to begin appropriate chemotherapy without delay.

REFERENCES

1. Patterson M, Healy GR, Shabot JM: Serologic testing for amoebiasis. Gastroenterology 78:136-141, Jan 1980

2. Communicable disease statistics. Los Angeles County Department of Health Services, 1980

3. Bruckner DA, Garcia LS, Voge M: Intestinal parasites in Los Angeles, California. Am J Med Technol 45:1020-1022, Dec 1979

4. Adams EB, MacLeod IN: Invasive amebiasis. Medicine (Baltimore) 56:315-334, Jul 1977

5. Krettek JP, Goldstein LI, Busuttil RW: The symptoms of an amebic abscess of the liver simulating an acute surgical abdomen. Surg Gynecol Obstet 148:552-556, Apr 1979

6. Wallace RJ, Greenberg SB, Lau JM, et al: Amebic peritonitis following rupture of an amebic liver abscess. Arch Surg 113:322-325, Mar 1978

7. Healy GR: Laboratory diagnosis of amebiasis. Bull NY Acad Med 47:478-493, May 1971

8. Krogstad DJ, Spencer HC, Healy GR: Current concepts in parasitology: Amebiasis. N Engl J Med 298:262-265, Feb 2, 1978

9. Perez JY: The management of amebic hepatic abscess. Drugs 15(Suppl 1):49-52, 1978

10. Shabot JM, Patterson M: Amebic liver abscess: 1966-1976. Dig Dis Sci 23:110-118, Feb 1978

11. Eggleston FC, Verghese M, Handa AK, et al: The results of surgery in amebic liver abscess: Experiences in eighty-three patients. Surgery 83:536-539, May 1978

12. Verlenden WL, Frey CF: Management of liver abscess. Am J Surg 140:53-59, Jul 1980

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Medical Progress

Operations for Management of Esophageal Variceal Hemorrhage

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Many surgical procedures, including four categories of portal-systemic shunts and a variety of nonshunting operations, have been proposed for patients who bleed from esophagogastric varices. As data have accumulated from clinical trials designed to assess these operations, no single procedure has emerged as ideal for all patients. The urgency of surgical operation, status of hepatic hemodynamics and experience of the surgeon appear to be the most important factors to consider in selecting the appropriate operation for a patient. The timing of the operation with respect to the acute bleeding episode remains controversial. As more effective, conservative methods for temporarily controlling hemorrhage have become available, however, most surgeons now prefer elective procedures because they have lower surgical mortality than emergency intervention. Selective portal-systemic shunts (distal splenorenal shunt and left gastric-vena caval shunt) and nonshunting operations are probably the only procedures that preserve hepatic portal perfusion and thus are less frequently complicated by postoperative encephalopathy than completely diverting shunts. Side-to-side portal-systemic shunts, because they decompress hepatic sinusoids and the splanchnic viscera, are the most effective operations for relieving ascites. None of the available procedures have been proved by controlled trials to be superior to others with respect to long-term postoperative survival.

THE MOST DRAMATIC and life-threatening complication of portal hypertension is hemorrhage from gastroesophageal varices. Although only a third of patients with varices ever bleed, once hemorrhage occurs the likelihood of recurrence exceeds 70 percent.[1-3] Mortality due to this complication has been reported to be from 22 percent[4] to 84 percent[5] and appears to be dependent on both the severity of the underlying liver disease and the effectiveness of the measures used to control hemorrhage. Several nonsurgical therapies, including aqueous vasopressin (Pitressin) infusion,[6,7] balloon tamponade,[8,9] transhepatic embolization of the coronary vein[10] and endoscopic variceal sclerosis[11-13] have been effective to variable degrees in controlling acute variceal bleeding; how-

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ABBREVIATION USED IN TEXT

BILG = Boston Interhospital Liver Group

ever, none of these treatments have been shown to confer long-term protection against recurrence of bleeding. Multiple surgical strategies have been devised, each with the hope that it would provide the definitive answer to this complex problem.

Operations for portal hypertension can be classified into two general categories, portal-systemic shunts and nonshunting procedures. Despite the fact that both of these surgical approaches have been applied during the past three decades, several areas of controversy remain. Do any of the available procedures prolong survival? Is any operation preferable to another with respect to postoperative mortality, morbidity or prevention of recurrent hemorrhage? When should emergency surgical intervention be used? What factors should be considered in selecting the appropriate operation for a patient who bleeds from esophageal varices?

The purpose of this review is to describe the surgical procedures available and to attempt to provide answers to the questions proposed above. Whenever possible, results from controlled studies will be emphasized in preference to noncontrolled studies or anecdotal experiences. Although points of controversy are almost certain to remain, it is hoped that the reader will gain a useful perspective of this difficult and complex clinical problem.

Portal-Systemic Shunt Operations

In 1877 the first portal-systemic shunt was done in a dog by Nicolai Eck, a young Russian military surgeon.[14] Eck showed not only that anastomosis of the portal vein to the inferior vena cava was technically possible but that the animal could survive with total diversion of portal venous flow. In the years following there were many other experimental and clinical experiences with this surgical approach, but the first consistently successful application of portal-systemic shunting to the clinical problem of portal hypertension must be attributed to Whipple[15] and Blakemore and Lord[16] who published their initial results in 1945. During the ensuing three decades, creative surgeons described and clinically tested a myriad of portal-systemic shunt operations. Despite their apparent complexity and diversity, all of these procedures can be classified into four hemodynamic categories (Figure 1):

- *end-to-side portacaval shunt*
- *several procedures in which a side-to-side communication is made between systemic and portal venous systems*
- *selective shunts that decompress only a component of the portal venous system*
- *end-to-side portacaval shunt in conjunction with arterialization of the intrahepatic portal venous tributaries*

End-to-Side Portacaval Shunt

The end-to-side portacaval shunt was the first shunt used clinically and, because of extensive experience with this procedure, it has become the prototype with which other modes of therapy are compared. Two hemodynamic alterations caused by the end-to-side portacaval anastomosis are total diversion of portal venous blood and decompression of the entire splanchnic venous bed. The liver becomes dependent on hepatic arterial flow and intrahepatic sinusoidal hypertension is frequently maintained by a compensatory increase in this flow. In 1966 a review of the medical literature, which included 154 separate reports, attested to the effectiveness of the portacaval shunt in that variceal hemorrhage recurred in only 2.8 percent of patients who had this procedure.[17] In fact, the early results were so encouraging that portacaval shunting became the procedure of choice for controlling variceal hemorrhage. It was not until the late 1950's that clinical investigators began to seriously question whether this operation benefited the quality or length of life of cirrhotic patients.

The portacaval shunt is the only surgical procedure for portal hypertension that has been extensively compared with nonsurgical therapy in randomized, controlled studies. The initial trials compared the prophylactic portacaval shunt (done in patients with varices that have not previously bled) with medical therapy. All four controlled trials of the prophylactic portacaval shunt failed to show an advantage in survival for the surgically treated patients.[18-20] In fact, two of the studies suggested that prophylactic operations detrimentally affect long-term survival.[19,20] The conclusion from these trials is that prophylactic portal-systemic shunts are no longer indicated.

Four randomized trials, three in this country[1,2,21] and one in France,[3] have compared nonsurgical

TABLE 1.—*Randomized Studies of the Therapeutic Portacaval Shunt*

	Therapy	No. of Cases	Survival (percent)	Recurrence of Bleeding (percent)	Encephalopathy (percent)
VA Cooperative[2] (5-year follow-up) ..	Shunt	78	57	9	32
	Medical	77	36	65	43
BILG[1] (5-year follow-up)	Shunt	25	65	9	48
	Medical	25	48	70	52
USC[21] (11-year follow-up)	Shunt	45	36	infrequent	35
	Medical	44	18	frequent	0
France[3] (3-year follow-up)	Shunt	40	47	8	40
	Medical	49	56	72	44

therapy with the therapeutic portacaval shunt (a procedure carried out electively in patients who have previously bled from varices). The patients in all four of these studies were almost exclusively patients with alcoholic cirrhosis. The end-to-side portacaval shunt was the only surgical procedure used in three of the trials,[2,3,21] while both end-to-side and side-to-side portacaval shunts were done in the fourth study.[1] Survival, frequency of recurrence of bleeding from esophageal varices and incidence of postoperative encephalopathy in each of these four investigations are summarized in Table 1. All three American trials showed increased survival for the patients with shunts, but in no instance does the increase reach statistical significance. However, the difference in survival between the surgical and medical groups in the Veterans Administration Cooperative[2] and the Boston Interhospital Liver Group (BILG)[1] studies comes very close to being statistically significant. The shorter survival period in both surgically and medically treated patients in the University of Southern California study can be accounted for by the longer follow-up (up to 11 years) in that trial.[21] The decreased survival rate of surgically treated patients in the French study is probably due to the relatively high surgical mortality of 20 percent despite the fact that only patients with "good" liver function were selected for that trial.[3] In all of the studies the most common cause of death in medically treated patients was recurrent hemorrhage, while patients treated with the portacaval shunt had a higher incidence of death from hepatic failure.

In all four studies recurrent variceal hemorrhage was uncommon in patients with shunt and generally occurred only in those with a portacaval shunt thrombosis. In contrast, approximately 70 percent of medically treated patients had recurrence of bleeding. Although total postoperative encephalopathy was no more common in the patients with shunts than in medically treated patients in three of the trials, severe encephalopathy was mainly confined to the surgical groups.[1-3] The main encephalopathy-precipitating factors for surgically and medically treated patients were protein ingestion and gastrointestinal hemorrhage, respectively. The most convincing evidence that portacaval shunting leads to psychoneurologic disturbances can be found in one of the prophylactic portacaval shunt studies in which severe, chronic encephalopathy developed in 20 percent of the patients with shunts as compared with only 3 percent of the medically treated patients ($P<0.01$).[22]

The following conclusions can be drawn from the results of these four important trials: Portacaval shunts, as long as they remain patent, prevent recurrent variceal hemorrhage; patients with a shunt probably live longer than medically treated patients (though this point has not been proved statistically); and quality of life following a portacaval shunt procedure is compromised in a significant number of patients by debilitating postoperative encephalopathy. The limitations of these studies should be considered when interpreting their results and conclusions. First, the portacaval shunt was the only operation used; the other surgical procedures that are discussed later in this review have yet to be compared with nonsurgical treatment in randomized trials. Second, with few exceptions only patients with alcoholic cirrhosis were studied. Since alcoholic cirrhosis has a very lethal natural history,[23,24] it is conceivable that prevention of variceal hemorrhage with a portacaval shunt in patients with nonalcoholic cirrhosis or noncirrhotic portal hypertension (for example, schistosomiasis) may result in longer survival. Finally, in all four studies portacaval shunts were done in the medical group when recurrent variceal hemorrhage was life threatening and could not be

controlled by medical means. Therefore, survival of many patients in the medical control group was dependent on the surgical procedure being tested.

The complete portal venous diversion and decompression that make the portacaval shunt so effective in preventing variceal hemorrhage are also the factors that lead to the adverse sequelae from this procedure. Several experimental studies with animals have conclusively shown that complete shunting of portal blood away from the liver is detrimental to hepatic and cerebral function.[25,26] Portal blood contains hepatotropic factors that are essential for maintenance of liver function and for hepatic regeneration.[27,28] Complete shunting results in direct delivery of these factors into the systemic circulation and their reappearance at the liver in a much diluted state. The consequences of these physiologic alterations may be liver atrophy and eventual hepatic failure. Therefore, as newer operations for portal hypertension have been developed, an emphasis has been placed on retention of hepatic portal per-

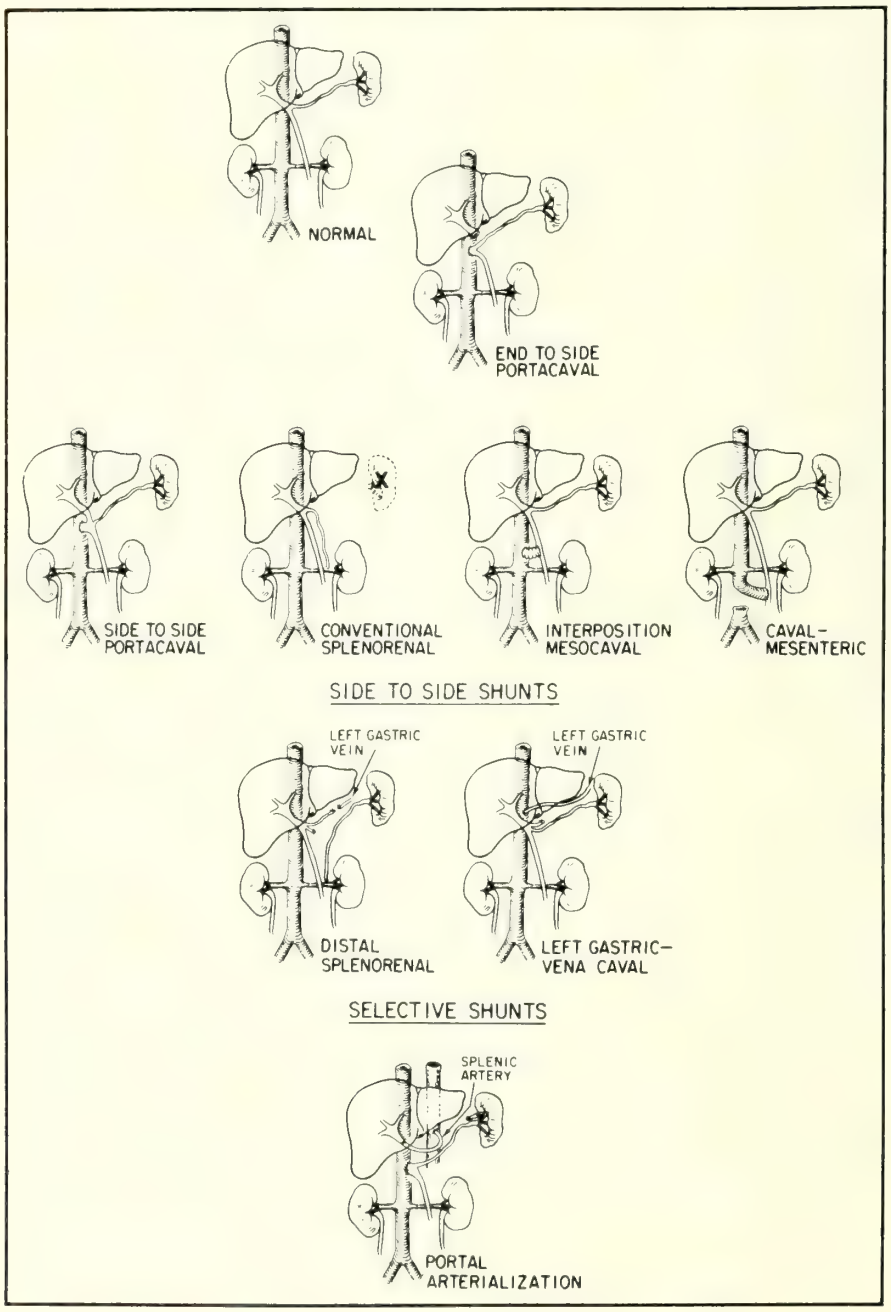

Figure 1.—Techniques of portal-systemic anastomosis (specific operations are described in the text).

fusion along with adequate variceal decompression.

Side-to-Side Portal-Systemic Shunts

Several techniques have been described for creating a side-to-side communication between portal and systemic venous systems (Figure 1). The objective of each of these procedures has been to incompletely decompress the portal venous circulation, thereby allowing continued portal perfusion of the liver. However, most of the evidence indicates that whenever a side-to-side anastomosis is of sufficient caliber to remain patent, complete portal venous diversion results.[29-31] Because the portal vein is left in continuity in all of these procedures, side-to-side shunts decompress the intrahepatic portal network and the splanchnic venous system. Intrahepatic sinusoidal hypertension plays a key role in the pathogenesis of ascites, so that side-to-side portal-systemic shunts are generally more reliable for relieving intractable ascites than the end-to-side portacaval shunt. Likewise, when the portal vein functions as a major outflow tract for the liver, such as in the Budd-Chiari syndrome and in spontaneous reversal of portal blood flow in cirrhosis, a side-to-side shunt is the surgical procedure of choice.[32]

Side-to-side portacaval shunt. Noncontrolled comparisons of side-to-side and end-to-side portacaval shunts suggest that the side-to-side procedure is more reliable in relieving and preventing ascites[33] and is associated with a lower surgical mortality in patients with poor hepatic function at the time of surgery.[34] The reported disadvantages of the side-to-side portacaval shunt are its relative technical difficulty and the higher incidence of portal-systemic encephalopathy postoperatively as compared with the end-to-side anastomosis.[35,36] Analyses of postoperative hepatic hemodynamics have shown that the side-to-side portacaval shunt diverts the entire portal venous flow in nearly all patients.[31,37,38] In addition, several studies have shown that the side-to-side anastomosis results in a fraction of hepatic arterial blood exiting the liver through the hepatic limb of the portal vein rather than through hepatic veins.[31,37,38] A variable fraction of this short-circuited hepatic arterial flow perfuses sinusoids during its transit through the liver.[38] The potentially greater decrease in nutrient blood flow resulting from this diversion of hepatic arterial blood may be the cause of the higher frequency of encephalopathy observed by some investigators following the side-to-side portacaval shunt. However, in the only controlled trial comparing the end-to-side and side-to-side portacaval shunts, no important differences could be detected with respect to either postoperative encephalopathy or survival.[1]

The side-to-side portacaval shunt was used in the past in nonbleeding patients with intractable ascites,[33] but now most of these patients are being successfully treated with either salt restriction alone or in combination with diuretic therapy. The few remaining patients with truly intractable ascites should undergo peritoneovenous shunting, a much less formidable operation than the side-to-side portacaval shunt.[39]

Conventional splenorenal shunt. The conventional splenorenal shunt is constructed by anastomosis of the proximal splenic vein to the left renal vein after removal of the spleen. Early noncontrolled studies suggested a lower frequency of encephalopathy following the splenorenal shunt than after the portacaval shunt, an advantage that was offset by a higher rate of recurrence of variceal hemorrhage in splenorenal shunt patients.[17] Both the low incidence of encephalopathy and the high rate of recurrent hemorrhage in these studies are most likely due to relatively more frequent thrombosis of the splenorenal anastomosis. Since the proximal splenic vein is usually very small in diameter, some surgeons feel that more reliable shunt patency can be achieved by a side-to-side anastomosis of the larger distal splenic vein to the left renal vein.[40] Although no randomized trial has been conducted to compare the conventional splenorenal shunt with other procedures, two recent investigations, one prospective[41] and one retrospective,[42] failed to show significant differences between splenorenal and portacaval shunt patients with respect to postoperative encephalopathy or survival other than the higher rates of shunt thrombosis and recurrent variceal hemorrhage in patients with splenorenal shunts. Yet another retrospective study of mainly patients with nonalcoholic cirrhosis revealed a substantially lower incidence of encephalopathy following the splenorenal shunt than after the portacaval shunt.[43] Postoperative shunt patency was not assessed in this trial.

Several studies suggest that a splenorenal shunt of large enough caliber to remain patent functions as a peripheral side-to-side portal-systemic shunt and diverts the entire portal venous blood flow. First, relief of ascites after a splenorenal shunt is

similar to that observed after a side-to-side portacaval shunt, which clearly diverts the entire portal venous blood flow. Assessment of hepatic hemodynamics has revealed a sharp decrease in both hepatic blood flow and portal venous pressure after a splenorenal shunt,[41] indicating a totally decompressing shunt. Finally, angiographic evaluation has failed to show continuing portal perfusion after a splenorenal anastomosis.[41]

An advantage of the splenorenal shunt combined with splenectomy is relief of hypersplenism. In the small number of patients with portal hypertension who have significant thrombocytopenia (persistent platelet counts $<50{,}000$ per cu mm) splenectomy is indicated because portal decompression alone does not reliably relieve hypersplenism.[44]

Interposition shunts. Interposing a synthetic graft between the splanchnic and systemic venous systems was popularized by Lord and co-workers[45] in 1970. Since then interposition grafts have been used in the portacaval, mesocaval, mesorenal, and splenorenal positions.[46] Because of the relative technical ease of constructing an interposition mesocaval shunt and because of initial favorable reports of this procedure by Drapanas and co-workers,[47,48] the mesocaval shunt is now one of the most common operations performed in this country for bleeding esophageal varices. Drapanas[48] reported a surgical mortality of 9 percent, a frequency of postoperative encephalopathy of 11 percent, a projected five-year survival rate of 70 percent, and angiographic evidence of continuing hepatic portal perfusion in 44 percent of patients following this procedure. However, two randomized trials comparing the interposition shunt with the distal splenorenal shunt have failed to duplicate Drapanas's excellent results.[49-51] In these studies the frequency of postoperative encephalopathy has approximated 50 percent, and careful assessment of postoperative hepatic hemodynamics indicated that no one with patent mesocaval shunts had continuing portal perfusion of the liver. In Drapanas's series the apparently high frequency of postmesocaval shunt hepatopetal (towards the liver) portal blood flow is probably due to a misinterpretation of the postoperative angiograms.[30]

Another disadvantage of interposition shunts is a high rate of shunt thrombosis. Smith and associates[46] reviewed their series of mesocaval, portacaval, mesorenal and splenorenal interposition grafts and discovered a shunt thrombosis rate of 24 percent. Ninety percent of shunt occlusions occurred in the late postoperative period.

Thus, the interposition mesocaval and other interposition shunts appear to be hemodynamically similar to the side-to-side portacaval shunt, but they have the considerable disadvantage of a higher frequency of shunt thrombosis. When a side-to-side portal-systemic shunt is indicated because of intractable ascites or spontaneous reversal of portal venous blood flow and previous surgery in the upper abdomen, or portal vein thrombosis makes the portal vein unavailable for anastomosis, the interposition mesocaval shunt is a reasonable alternative. Similarly, an interposition portacaval shunt is preferable to excision of liver tissue when an enlarged caudate lobe makes a side-to-side portacaval anastomosis difficult.

Caval mesenteric shunt. The caval mesenteric shunt, which is constructed by direct anastomosis of the divided inferior vena cava to the superior mesenteric vein, was independently described by Clatworthy and co-workers[52] and Marion.[53] Because severe leg edema develops in a significant percentage of adults after division of the inferior vena cava, this procedure is done only in children with extrahepatic portal hypertension. The major advantage of this technique is that a large diameter vein-to-vein anastomosis can be accomplished. Splenorenal shunts in children often occlude because of the small size of the splenic vein. Voorhees and Price[54] found that the caval mesenteric shunt was followed by recurrent variceal hemorrhage in only 13 percent of children as contrasted to 44 percent and 79 percent after splenorenal and makeshift shunts, respectively. Despite the fact that most of the patients in this series had extrahepatic portal hypertension and normal livers, 29 percent had evidence of cerebral dysfunction after caval mesenteric shunting. Although refined hemodynamic studies after a caval mesenteric shunt have not been carried out this anastomosis likely functions as a side-to-side portacaval shunt and diverts the entire portal venous flow away from the liver. Since the introduction of the interposition mesocaval shunt, few caval mesenteric shunts have been done.

Selective Portal-Systemic Shunts

The objective of selective portal-systemic shunts is to decompress the variceal-bearing gastrosplenic venous circulation, while maintaining high pressure and hepatopetal flow in the rest of the portal venous system. Claims of selectivity have

TABLE 2.—*Randomized Studies of the Distal Splenorenal Shunt*

	Shunt	No. of Patients	Survival (percent)	Shunt Occlusion (percent)	Encephalopathy	Portal Perfusion (percent)
Atlanta Study[49]	DSR	(26)	62	10	12%	88
	Interposition mesocaval	(29)	72	18	52%	0
Philadelphia Study[50,51]	DSR	(13)	62	0	.75 month	86
	Interposition mesocaval	(14)	71	14	3.75 months	0
Toronto Study[56]	DSR	(22)	67	..	14%	..
	PCS	(21)	68	..	50%	..

DSR = distal splenorenal, PCS = portacaval shunt.

been made for several of the previously described side-to-side portal-systemic shunting procedures, but only the distal splenorenal and left gastric-vena caval shunts have been shown convincingly to function as selective portal-systemic shunts (Figure 1).

Distal spenorenal shunt. The distal splenorenal shunt was introduced as a treatment for variceal hemorrhage by Warren and associates in 1967.[55] This procedure consists of anastomosis of the distal end of the divided splenic vein to the left renal vein and interruption of all collateral pathways, such as the left gastric and right gastroepiploic veins that connect the gastrosplenic and superior mesenteric components of the splanchnic venous system. In contrast to the conventional splenorenal shunt, which includes splenectomy, an intact spleen is essential for a functional distal splenorenal shunt.

Certain criteria should be met before choosing the distal splenorenal shunt for a person who has bled from varices. Because one of the main objectives of this procedure is preservation of hepatic portal perfusion, hepatopetal portal venous flow should be demonstrable on preoperative visceral angiograms. Anatomic requirements include a splenic vein of adequate size (greater than 8 mm) and a favorable anatomic relationship of splenic and left renal veins. Finally, since the distal splenorenal shunt does not relieve hepatic sinusoidal or superior mesenteric venous hypertension, it is a poor choice for patients with medically intractable ascites. However, patients in whom ascites transiently develops during resuscitation from a variceal hemorrhage or patients who previously had ascites that improved with diuresis are acceptable candidates for this procedure.

Although no controlled study has been done to contrast the distal splenorenal shunt with nonsurgical therapy, four randomized trials have been conducted, two[49,50] comparing the distal splenorenal and interposition mesocaval shunts and two[56,57] comparing the distal splenorenal and end-to-side portacaval shunts. Only preliminary results are available in one of these studies,[57] but the three trials[49,50,56] have been completed, the results of which are summarized in Table 2. While long-term survival has been similar with the two shunts tested in each of the studies, postoperative encephalopathy has been less frequent and maintenance of hepatic portal perfusion has been greater with the distal splenorenal shunt. In the early postoperative period, hepatopetal portal venous flow was evident after the distal splenorenal shunt in 88 percent and 86 percent of patients in the Atlanta[49] and Philadelphia[51] trials, respectively. In contrast, no one with a patent interposition shunt had evidence of hepatic portal perfusion in either study. Quantitative measurement of portal blood flow showed a mean decrease of only 30 ml a minute after the distal splenorenal shunt, whereas nearly all patients had reversal of portal venous flow after the mesocaval shunt.[51] Portal-systemic encephalopathy was a frequent occurrence after interposition mesocaval and portacaval shunts (occurring in approximately 50 percent of patients), while this complication occurred in less than 15 percent of patients following the distal splenorenal shunt.[49,50,56] Loss of portal blood flow and the development of encephalopathy appeared to be related, since no patient with continuing portal perfusion in the late postoperative period had either clinical or electroencephalographic evidence of encephalopathy in the Atlanta trial.[49] In contrast to the three complete studies,[49,50,56] the Boston-New Haven trial[57] comparing the distal splenorenal and end-to-side portacaval shunts has so far shown no substantial differences between these procedures in either survival or postoperative encephalopathy. However, postoperative follow-up is brief and hepatic hemodynamics have not been assessed in this study.

Two nonrandomized studies[58,59] have also re-

ported excellent results in patients in whom the distal splenorenal shunt procedure was done. In a matched-control study Busuttil and co-workers[58] found that the distal splenorenal shunt resulted in a considerably lower incidence of encephalopathy and a longer survival than the end-to-side portacaval shunt. Zeppa and associates[59] reported a remarkable five-year survival rate of 89 percent in patients with nonalcoholic cirrhosis following the distal splenorenal shunt procedure. Because all of the studies published to date have been only on cirrhotic patients, the results of a controlled study of the distal splenorenal shunt in patients with noncirrhotic portal hypertension (schistosomiasis) are eagerly awaited.[60]

An important question regarding the distal splenorenal shunt is whether it maintains its selectivity in the late postoperative period. Several studies[49,61-63] have shown progressive loss of hepatopetal portal blood flow on serial postoperative angiograms after construction of a distal splenorenal anastomosis. In two of these investigations[62,63] the surgical procedure did not include ligation of collaterals (coronary and right gastroepiploic veins) between the superior mesenteric and gastrosplenic components of the portal venous system, which is an essential part of the operation as described by Warren.[64] However, even when the distal splenorenal shunt is performed as originally described, progressive portal-systemic collateralization occurs with time, as demonstrated by maintenance of hepatic portal perfusion in only 42 percent of patients in the late postoperative period, as compared to 88 percent of patients immediately after surgery in the Atlanta trial.[49] Whether this gradual loss of the hepatic portal blood supply will alter eventual clinical results remains to be determined.

Left gastric-vena caval shunt. The left gastric-vena caval shunt is a recently described procedure for selectively decompressing esophagogastric varices.[65] This operation is done either by direct anastomosis of the left gastric (coronary) vein to the inferior vena cava or by interposing a synthetic or vein graft between these two vessels. Inokuchi and co-workers,[65] the originators of this procedure, found it possible to construct a left gastric vein-vena caval anastomosis in 89 percent of patients in whom it was attempted. The 117 patients in their series all had nonalcoholic cirrhosis or noncirrhotic portal hypertension. The operation was used as a prophylactic measure in a third of these patients. Results in this group of patients have been excellent with a five-year survival rate of 78 percent, a low frequency of postoperative encephalopathy, a recurrence of variceal bleeding in 10 percent of patients and shunt patency proved by angiography or autopsy in 90 percent of patients. The left gastric-vena caval shunt has yet to be extensively tested in patients with alcoholic cirrhosis. However, this operation may not be technically possible in most patients with this diagnosis because the coronary vein is usually thin-walled and less than 1 cm in diameter.

End-to-Side Portacaval Shunt With Hepatic Arterialization

Arterialization of the hepatic portal vein has been proposed for maintaining liver blood flow with an end-to-side portacaval shunt.[66,67] Because hepatic arterialization causes sclerosis of intrahepatic portal vein tributaries in experimental animals,[68] proponents of this operation have generally preferred a small caliber vessel, such as the gastroepiploic[67] or splenic arteries,[66] for construction of the arterial-portal vein fistula. No data have yet been accumulated that would establish whether or not a relatively low-flow arterial-portal venous fistula has any adverse effects on intrahepatic portal vein branches. Experience with this procedure has been mainly confined to Europe[66] and one American institution,[67] and no randomized trial comparing this operation with other portal-systemic shunts has been conducted. In fact, not even a noncontrolled long-term follow-up of patients with hepatic arterialization has been reported. Angiographic evaluation of this procedure in a small number of patients a year postoperatively has revealed a high frequency of thrombosis of the arterial-portal venous fistula.[66] Even if fistula occlusion did not occur, a theoretic objection to hepatic arterialization is that portal hepatotropic factors are not restored.

Nonshunting Operations

Nonshunting operations for portal hypertension attempt to accomplish one or a combination of the following objectives: (1) actual obliteration of esophagogastric varices, (2) interruption of collateral pathways to varices, (3) decrease of blood flow into the portal venous system, and (4) promotion of portal-systemic collateralization. Because none of the nonshunting procedures result in substantial portal decompression, their major advantages are maintenance of hepatic portal perfusion and a low frequency of post-

operative encephalopathy. An important disadvantage is that most of these operations are followed by frequent recurrent variceal hemorrhage. None of the nonshunting procedures have been compared with either medical treatment or portal-systemic shunt operations by randomized controlled trials.

Ligation of Varices and Esophageal Transection

Because transthoracic ligation of varices[69] and esophageal transection with suture reanastomosis of the esophagus[70] have generally been performed on an emergency basis in patients with markedly compromised hepatic function, both procedures have been associated with surgical mortalities approaching 50 percent. The high frequency of recurrent variceal hemorrhage (30 percent to 50 percent) after these operations has led to their proponents recommending an elective portal-systemic shunt procedure in survivors.[69,70] Because the overall surgical mortality for this approach is the combined mortalities for the esophageal and shunting procedures, transesophageal ligation of varices and transthoracic esophageal transection are infrequently done. A simpler operative technique for obliterating esophageal varices is transection and reanastomosis of the lower esophagus with one of the recently developed stapling instruments.[71,72] As this procedure is performed through an abdominal incision, coronary vein ligation can also be accomplished. Preliminary reports[71,72] indicate lower morbidity and mortality after intraabdominal esophageal transection than after the transthoracic approach.

Esophagogastric Devascularization Combined With Splenectomy

Esophagogastric devascularization procedures in American patients with alcoholic cirrhosis have generally resulted in a high rate of recurrent variceal hemorrhage. Johnson and co-workers[73] devised a devascularization operation that consists of splenectomy, resection of the upper greater curvature of the stomach, left gastric artery ligation and intraluminal ligation of esophageal varices. Despite this extensive devascularization of upper stomach and esophagus, 50 percent of their patients had recurrence of bleeding during the postoperative period. Cooperman and Hermann[74] combined splenectomy with a variety of ligation procedures in 25 patients with alcoholic cirrhosis. Only 38 percent of their patients had long-term survival, and 100 percent of the survivors had recurrence of bleeding from esophageal varices. In contrast to the disappointing American experience with devascularization operations, a two-stage procedure recently developed in Japan has been more successful in preventing recurrent variceal hemorrhage.[75,76] However, the cases of portal hypertension in these Japanese studies have consisted mainly of good-risk patients with nonalcoholic cirrhosis and patients who had not previously bled from esophageal varices (prophylactic operation).[76] The first stage of the Sugiura procedure is done through a left thoracotomy incision and includes paraesophageal devascularization to the inferior pulmonary vein combined with esophageal transection and reanastomosis. In low-risk patients the abdominal stage of the operation, which includes splenectomy, lower esophageal and upper gastric devascularization and pyloroplasty, can be completed at the same time through a diaphragmatic incision. In poor-risk, acutely bleeding patients the second stage is usually completed at a later time through an abdominal incision. Sugiura's results with this operation have been excellent with an overall seven-year survival of 83 percent and recurrent variceal hemorrhage in only 4 of 276 patients.[76] However, whether these results can be duplicated in patients with alcoholic cirrhosis remains to be shown.

Splenic Artery Ligation

Possibly the least complicated surgical procedure for treatment of variceal hemorrhage is splenic artery ligation in combination with occlusion of the coronary vein.[77,78] In fact, with the angiographic techniques now available, both of these objectives can be achieved without surgical intervention. Although previous experience would suggest that elimination of splenic arterial flow is an ineffective means of decreasing portal venous pressure, Del Guercio and co-workers[77] and Witte and associates[78] have separately established criteria to define which patients might benefit from splenic artery ligation. Del Guercio[77] developed a method of intraoperatively estimating the splenic component of portal venous blood flow by measuring oxygen saturation in the splenic and portal veins. Six individuals who met his criteria had a mean reduction in portal venous pressure of 9 cm of water after splenic artery ligation, and only one patient has bled from varices postoperatively. Witte's selection criteria include a splenic artery diameter greater than 8 mm and a rapid arm-to-

spleen circulation time of technetium Tc 99m sulfur colloid.[78] The eight persons in his study had a mean reduction in portal venous pressure of 3.7 mm of mercury and two of the five patients, in whom splenic artery ligation was performed for management of variceal hemorrhage, had recurrence of bleeding postoperatively. The effectiveness of splenic artery ligation in preventing recurrence of bleeding from esophageal varices needs to be determined in a larger, controlled trial before wider application of this procedure.

Splenectomy

Although splenectomy alone has generally been ineffective in preventing recurrent variceal hemorrhage,[79] the one situation in which removal of the spleen is definitely preferable to a portal-systemic shunt is that of isolated splenic vein thrombosis without liver disease.[80] Splenic vein thrombosis is most frequently caused by chronic pancreatitis, but pancreatic carcinoma and coagulation disorders, such as polycythemia vera and paroxysmal nocturnal hemoglobinuria, may also lead to this condition. High venous pressures are confined to the gastrosplenic component of the splanchnic circulation while portal vein pressure remains normal; hence, splenectomy is curative when varices are caused by isolated splenic vein thrombosis.[80] This disorder can always be diagnosed preoperatively if visceral angiography is a routine part of the workup of patients who bleed from esophageal varices.

Promotion of Portal-Systemic Collateralization

The formation of portal-systemic collaterals in patients with portal hypertension can be enhanced by transposition of the omentum or spleen to the subcutaneous layer or by transposition of the spleen to the thorax. The earliest described operation for stimulation of portal-systemic collateralization was subcutaneous transposition of the omentum, and this procedure was mainly used for relief of ascites.[81] A much more recent experience with thoracic splenic transposition in 37 patients who had bled from varices showed that, although portal-systemic collaterals developed, recurrent hemorrhage occurred in two thirds of the patients.[82] Subcutaneous transposition of the partially resected spleen in eight patients resulted in recurrent variceal bleeding in two of the seven survivors.[83] All patients were relieved of hypersplenism following transposition of the spleen to a subcutaneous location. Because several months are required for development of collaterals, the transposition operations are applicable only to the elective situation. Much more experience is required to determine effectiveness in this limited setting.

Timing of Operations

Operations for variceal hemorrhage can be done at the following times with respect to the acute bleeding episode: (1) prophylactically, before hemorrhage has occurred, (2) electively, at some period after bleeding has been controlled by nonsurgical methods, and (3) emergently, during or shortly after an acute variceal hemorrhage. As previously discussed, prophylactic portal-systemic shunts are clearly not indicated because three randomized, controlled trials have failed to show that they prolong survival.[18-20] Therefore, the only remaining controversy is between surgeons who prefer elective surgical intervention whenever possible and those who believe that emergency surgical operations result in higher percentages of patient survival.

Proponents of elective surgery base their argument on the well-established relationship between status of liver function at the time of surgery and surgical mortality. Several studies have shown a close correlation between hepatic functional reserve, as measured by Child's classification or one of its modifications, and early postoperative survival in patients with cirrhosis.[42,84-86] The only other easily assessable variable that has been reported to be predictive of surgical outcome is the degree of acute hyaline necrosis detectable on liver biopsy in patients with alcoholic cirrhosis.[87,88] However, some investigators doubt the predictive value of liver biopsy.[50,85,89] Because hepatic function is adversely affected by variceal hemorrhage in most patients, a preoperative course of medical treatment to relieve ascites, encephalopathy or both and to enhance nutrition and improve hepatic function should result in improved chances of survival. This period of preparation also allows for more complete evaluation of the patient's disorder by visceral angiography and liver biopsy when indicated. A study has now shown that Child's classification can be considerably improved in most patients if an interval of medical management is interposed between the acute bleeding episode and surgical procedure.[4]

The elective surgical approach is based on the premise that effective nonsurgical techniques for control of variceal hemorrhage are available. The

medical methods used most frequently are vasopressin infusion, balloon tamponade and variceal sclerosis. If hemorrhage does not subside spontaneously or following gastric lavage, the first line of medical therapy in most institutions is vasopressin administration. Two recent randomized trials have shown that continuous peripheral intravenous administration of vasopressin is just as effective as selective, superior mesenteric arterial infusion.[6,7] Because it is less complicated and can be initiated much more rapidly, the intravenous route is usually preferred. In most series vasopressin is effective in controlling acute variceal hemorrhage in about half of the patients.[4,6,7] When vasopressin infusion fails or is contraindicated because of coexisting coronary artery disease, a more effective but riskier nonsurgical technique is variceal tamponade with a Sengstaken-Blakemore tube. Although considerable mortality and morbidity with the use of the Sengstaken-Blakemore tube have been reported,[90] several studies have shown that when a strict protocol is followed, balloon tamponade can be a safe and effective method for control of variceal hemorrhage.[4,8,9] Balloon tamponade is initially effective in 80 percent to 90 percent of patients with acute variceal bleeding and hemorrhage recurs in 20 percent to 40 percent of patients following balloon deflation.[4,8,9] In one study the combination of vasopressin and balloon tamponade resulted in control of hemorrhage in 69 percent of patients, allowing time for hepatic function to improve so that eventual surgical intervention had minimal postoperative mortality.[4]

Patients who continue to bleed from varices despite vasopressin infusion, balloon tamponade or both may be candidates for induction of either endoscopic variceal sclerosis or transhepatic coronary vein embolization. Although first introduced in 1939,[91] there has been a recent resurgence of interest in endoscopic variceal sclerosis. Whether rigid[11,12] or flexible[13] endoscopes are used, initial control of hemorrhage with this technique has been in the 85 percent to 95 percent range. Although rebleeding rates have been quite high in some series,[11,92] other investigators have adopted induction of variceal sclerosis as a definitive, long-term method for control of bleeding varices.[13,93] Whether their initial enthusiasm is warranted remains to be determined by controlled comparisons of variceal sclerosis with currently available surgical approaches. Percutaneous transhepatic embolization of the coronary vein was introduced by Lunderquist and Vang in 1974,[94] and several groups have since applied this technique to acutely bleeding patients with varying degrees of success.[10,95,96] Although initial control of hemorrhage has been quite good in some series, high rates of later recurrence of bleeding have suggested that transhepatic coronary vein embolization provides only temporary rather than definitive control of variceal hemorrhage.[10,95]

Because of excessive mortality ranging from 20 percent to 73 percent following emergency surgery,[97] there are few remaining advocates of this approach to control of acute variceal bleeding. The proponents of emergency surgery argue that the nonsurgical methods discussed above are generally ineffective and result in higher mortality than routine emergency surgical intervention in these poor-risk, acutely bleeding patients. Orloff and associates[98] have reported an experience with emergency portacaval shunts in 180 randomly selected, consecutive patients with cirrhosis and bleeding esophageal varices. Surgical mortality was 42 percent, and 38 percent of patients have survived five years in this series. The high surgical mortality reported by Orloff was justified by comparing it to a mortality of greater than 80 percent in a "control group" of medically treated patients from the early 1960's.[5] However, the death rate during a limited preoperative period of medical management would almost certainly be lower today.[4,99] Although the appropriate controlled studies comparing emergency with elective surgery have not been done, the success of available nonsurgical methods in temporarily controlling variceal bleeding in most patients would support a policy of selective rather than emergency surgery in this high-risk population.

Selection of Surgical Procedure

There is no single surgical procedure that is ideal for all patients who hemorrhage from esophagogastric varices. Alternatives include one of the three types of portal-systemic shunts and a variety of nonshunting procedures (Table 3). The most important factors that aid in selecting the appropriate operation are: clinical situation, status of hepatic hemodynamics and experience and skill of the surgeon.

The two main clinical factors that bear on selection of the operative approach are the urgency of the situation and the presence or absence of ascites. If uncontrolled variceal hemorrhage necessitates emergency surgical intervention, the

TABLE 3.—*Operations for Portal Hypertension*

	Portal Perfusion	*Encephalopathy*	*Control of Ascites*	*Control of Bleeding*
End-to-side portacaval shunt	none	frequent	fair	excellent
Side-to-side shunts (many varieties)	none	frequent	excellent	good
Distal splenorenal shunt	preserved	infrequent	poor	excellent
Nonshunting procedures	preserved	infrequent	fair	poor

technically easiest procedure with the greatest reliability for controlling bleeding should be done. Probably the most frequently used portal-systemic shunting procedures in the emergency setting are the end-to-side portacaval shunt and the interposition mesocaval shunt. Malt and co-workers[100] compared these two operations in patients requiring emergency portal decompression and found surgical mortality of 46 percent and 73 percent for portacaval and mesocaval shunt groups, respectively. These results, although not substantially different, combined with the known higher rate of late shunt occlusion in patients with interposition grafts,[46,86] make the end-to-side portacaval shunt a suitable choice for the acutely bleeding patient. When the clinical situation is urgent rather than emergent and preoperative angiography can be completed safely, the technically more demanding distal splenorenal shunt should be considered for patients who meet the other criteria for this procedure. The benefit to patients is a lower likelihood that postoperative encephalopathy will develop.[49,50,56]

Because of the excessive surgical mortality associated with emergency shunt procedures of all types in poor-risk patients,[97,98] many surgeons have preferred nonshunting procedures in the emergency situation. Transthoracic ligation of varices and extensive intraabdominal devascularization procedures are also accompanied by considerable surgical morbidity and mortality in the emergency setting,[69,70] so that esophageal transection and reanastomosis with an automatic stapling gun have recently been proposed to control variceal hemorrhage.[71,72] Experience with this new surgical approach is limited, however, and larger clinical trials are required to determine its effectiveness.

Ascites develops in most patients with cirrhosis following resuscitation from a major variceal hemorrhage. If the ascites resolves with conservative measures, the surgical procedure that would otherwise be appropriate for that patient should be selected. When ascites is intractable to medical management, however, one of the varieties of side-to-side portal-systemic shunts should be performed, because these are the only procedures that decompress both the splanchnic viscera and hepatic sinusoids, the sites of ascites formation. When anatomically possible, a direct side-to-side portacaval shunt is preferable because of its high long-term patency rate.

Hepatic hemodynamics and portal venous anatomy can be assessed from preoperative visceral angiograms. An angiographic "liver package" consists of selective injections of superior mesenteric, splenic and hepatic arteries; visualization of the left renal vein with contrast dye; and measurement of hepatic venous wedge pressure.[101,102] Hepatic portal perfusion is considered to be present when the main portal vein and intrahepatic tributaries are seen during the venous phase of the superior mesenteric arterial injection. Analysis of the angiogram provides only a qualitative index of hepatic portal perfusion. Therefore, a recently described radiocolloid technique, which can be done in conjunction with angiography and which quantifies the portal-systemic shunt fraction, can be a useful adjunct for evaluating hepatic hemodynamics.[29,103] Inability to see the portal vein following superior mesenteric arterial injection suggests either portal vein thrombosis or reversal of portal venous blood flow. If the portal vein is seen during the venous phase of the hepatic arterial injection, the diagnosis of reversal of portal venous blood flow is confirmed.[30] The venous phase of the splenic arterial injection and left renal venography aid in determining relative position, size and anatomic variations of these veins when a splenorenal shunt is contemplated. Although an elevated hepatic venous wedge pressure is diagnostic of portal hypertension, the magnitude of the pressure does not help select the surgical procedure.[104]

In some centers portal venous anatomy and hemodynamics are assessed with direct injection of contrast medium into the portal venous system, by means of splenoportography,[105] umbilical venography[106] or percutaneous transhepatic portography.[107] These techniques are more invasive

than visceral angiography and are therefore associated with a greater risk of complications, but they result in good definition of venous anatomy and the ability to directly evaluate the direction of portal flow.

When hepatopetal portal blood flow can be shown by one of the techniques described above, the distal splenorenal shunt is the operation of choice for most patients because it is the only portal-systemic shunting procedure (except the left gastric-vena caval shunt) that preserves portal blood flow.[49,51] The benefit to the patient is a lower likelihood that postoperative encephalopathy will develop, which occurs in only 10 percent to 15 percent of individuals after the distal splenorenal shunt procedure, in contrast to 40 percent to 50 percent of patients following shunt procedures that cause total diversion.[49,50,56] When hepatic portal perfusion is present and a distal splenorenal shunt cannot be constructed because of prior splenectomy or aberrant anatomy, either one of the nonshunting procedures, which also preserve portal blood flow, or a total shunt must be considered. The major disadvantage of nonshunting operations is that they are associated with a high frequency of recurrent variceal hemorrhage.

In patients with diffuse splanchnic venous thrombosis and no major portal tributaries available for anastomosis, a nonshunting procedure may be the only operation possible. Attempts at constructing makeshift shunts in these patients are generally unsuccessful. Isolated portal vein thrombosis in patients without liver disease presents a special situation. These persons, who are usually children, generally have substantial hepatic portal perfusion through hepatopetal portal collaterals. A completely diverting shunt (for example, mesocaval) results in loss of portal blood flow and a high frequency of postoperative encephalopathy. Patients with isolated portal vein thrombosis are therefore good candidates for a distal splenorenal shunt.[108]

If preoperative angiography or other hemodynamic studies reveal minimal or absent hepatic portal perfusion, and spontaneous reversal of portal blood flow is not present, an end-to-side portacaval shunt is a reasonable surgical approach because it results in little further alteration of already compromised hepatic hemodynamics. When preoperative studies reveal spontaneous reversal of portal blood flow, however, a side-to-side portal-systemic shunt procedure is mandatory. Construction of an end-to-side portacaval or distal splenorenal shunt in this situation could result in intractable ascites.

In the rare patient with considerable hypersplenism (persistent platelet counts of less than 50,000 per cu mm or leukocyte counts less than 2,000 per cu mm), splenectomy should be included with whatever operation is selected because neither total portal nor isolated splenic decompression reliably relieves hypersplenism.[44] Splenectomy can be conveniently done in association with either the conventional splenorenal shunt procedure or one of the nonshunting operations.

The experience and competence of the surgeon is possibly the most important factor in selecting the surgical procedure for a patient who has bled from esophageal varices. In making the choice surgeons should consider only those procedures with which they are familiar. Attempting a new and difficult operation without experienced and competent assistance all too often results in disaster. Of the commonly carried out operations, the end-to-side portacaval shunt, the interposition mesocaval shunt and nonshunting procedures are considered to be technically easier than the side-to-side portacaval and distal splenorenal shunts. In a patient with portal hypertension, however, any of these procedures can be formidable for even the most experienced hands. A major objection to the distal splenorenal shunt has been its relative technical difficulty. However, several surgical groups have proved that with appropriate training the distal splenorenal shunt procedure may be done without resulting in initially high shunt failure rate and mortality. Finally, if optimal results are to be obtained, it is essential that gastroenterologists and radiologists with expertise and interest in the area of portal hypertension participate with the surgeons in the care of these challenging patients.

No randomized, controlled trial has yet shown an advantage of one surgical procedure over another with respect to long-term survival. If the patient population consists predominantly of those with alcoholic cirrhosis, all operations appear to result in a 40 percent to 60 percent five-year survival. The relatively rapid progression of liver disease in patients with alcoholic cirrhosis is probably the main factor determining survival and overrides any potential benefits of the surgical procedures. However, it is hoped that length of survival will improve in patients with nonalcoholic

cirrhosis and noncirrhotic portal hypertension when the procedure chosen is tailored to the specific clinical and hemodynamic circumstances of each patient.

REFERENCES

1. Resnick RH, Iber FL, Ishihara AM, et al: A controlled study of the therapeutic portacaval shunt. Gastroenterology 67: 843-857, 1974

2. Jackson FC, Perrin EB, Felix R, et al: A clinical investigation of the portacaval shunt: V. Survival analysis of the therapeutic operation. Ann Surg 174:672-701, 1971

3. Rueff B, Prandi D, Degos F, et al: A controlled study of therapeutic portacaval shunt in alcoholic cirrhosis. Lancet 1:655-659, 1976

4. Holman JM, Rikkers LF: Success of medical and surgical management of acute variceal hemorrhage. Am J Surg 140:816-820, 1980

5. Orloff MJ: Emergency treatment of bleeding esophageal varices in cirrhosis, *In* Longmire WP Jr (Ed): Portal Hypertension. Curr Probl Surg, Jul 1966, pp 13-28

6. Johnson WC, Widrich WC, Ansell JE, et al: Control of bleeding varices by vasopressin: A prospective randomized study. Ann Surg 186:369-376, Sep 1977

7. Chojkier M, Groszmann RJ, Atterbury CE, et al: A controlled comparison of continuous intraarterial and intravenous infusions of vasopressin in hemorrhage from esophageal varices. Gastroenterology 77:540-546, Sep 1979

8. Pitcher JL: Safety and effectiveness of the modified Sengstaken-Blakemore tube: A prospective study. Gastroenterology 61:291-298, 1971

9. Bauer JJ, Kreel I, Kark AE: The use of the Sengstaken-Blakemore tube for immediate control of bleeding esophageal varices. Ann Surg 179:273-277, 1974

10. Bengmark S, Börjesson B, Hoevels J, et al: Obliteration of esophageal varices by PTP: A follow-up of 43 patients. Ann Surg 190:549-554, Oct 1979

11. Johnston GW, Rodgers HW: A review of 15 years' experience in the use of sclerotherapy in the control of acute haemorrhage from oesophageal varices. Br J Surg 60:797-800, Oct 1973

12. Terblanche J, Northover JMA, Bornman P, et al: A prospective evaluation of injection sclerotherapy in the treatment of acute bleeding from esophageal varices. Surgery 85:239-245, 1979

13. Lewis J, Chung RS, Allison J: Sclerotherapy of esophageal varices. Arch Surg 115:476-481, 1980

14. Eck NV: On the question of ligature of the portal vein. Voyenno-Med 130:1-2, 1877

15. Whipple AO: The problem of portal hypertension in relation to the hepatosplenopathies. Ann Surg 122:449-475, 1945

16. Blakemore AH, Lord JW Jr: The technic of using vitalium tubes in establishing portacaval shunts for portal hypertension. Ann Surg 122:476-488, 1945

17. Grace ND, Muench H, Chalmers TC: The present status of shunts for portal hypertension in cirrhosis. Gastroenterology 50: 684-691, 1966

18. Resnick RH, Chalmers TC, Ishihara AM, et al: The Boston Interhospital Liver Group: A controlled study of the prophylactic portacaval shunt—A final report. Ann Intern Med 70:675-688, Apr 1969

19. Jackson FC, Perrin EB, Smith AG, et al: A clinical investigation of the portacaval shunt—II. Survival analysis of the prophylactic operation. Am J Surg 115:22-42, 1968

20. Conn HO, Lindenmuth WW, May CJ, et al: Prophylactic portacaval anastomosis—A tale of two studies. Medicine (Baltimore) 51:27-40, Apr 1972

21. Reynolds T, Donovan A, Mikkelsen W, et al: Results of an 11-year randomized trial of end-to-side portacaval shunt in patients with alcoholic liver disease (Abstract). Gastroenterology 75:982, 1978

22. Mutchnick MG, Lerner E, Conn HO: Portal-systemic encephalopathy and portacaval anastomosis: A prospective, controlled investigation. Gastroenterology 66:1005-1019, May 1974

23. Ratnoff OD, Patek AJ: The natural history of Laennec's cirrhosis of the liver. Medicine (Baltimore) 21:207-262, 1942

24. Garceau AJ, Chalmers TC, and Boston Inter-Hospital Liver Group: The natural history of cirrhosis—I. Survival with esophageal varices. N Engl J Med 268:469-473, 1963

25. Hahn M, Massen O, Nencki M, et al: Die Eck'sche Fistel zwischen der unteren Holvene und der Pfortader und ihre Folgen für den Organismus. Arch Exp Pathol Pharmokol 32:162-210, 1893

26. Marchioro TL, Porter KA, Brown BI, et al: The effect of partial portacaval transposition on the canine liver. Surgery 61: 723-732, 1967

27. Starzl TE, Francavilla A, Halgrimson CG, et al: The origin, hormonal nature, and action of hepatotrophic [sic] substances in portal venous blood. Surg Gynecol Obstet 137:179-199, Aug 1973

28. Fisher B, Szuch P, Levine M, et al: The intestine as a source of a portal blood factor responsible for liver regeneration. Surg Gynecol Obstet 137:210-214, 1973

29. Rikkers LF, Miller FJ, Christian P: Effect of portasystemic shunt operations on hepatic portal perfusion. Am J Surg 141: 169-174, 1981

30. Fulenwider JT, Nordlinger GM, Millikan WJ, et al: Portal pseudoperfusion: An angiographic illusion. Ann Surg 189:257-268, 1979

31. Redeker AG, Kunelis CT, Yamamoto S, et al: Assessment of portal and hepatic hemodynamics after side-to-side portacaval shunt in patients with cirrhosis. J Clin Invest 43:1464-1471, 1964

32. Warren WD, Muller WH: A clarification of some hemodynamic changes in cirrhosis and their surgical significance. Ann Surg 150:413-427, 1959

33. Burchell AR, Rousselot LM, Panke WF: A seven-year experience with side-to-side portacaval shunt for cirrhotic ascites. Ann Surg 168:655-670, Oct 1968

34. Turcotte JG, Wallin VW Jr, Child CG III: End to side versus side to side portacaval shunts in patients with hepatic cirrhosis. Am J Surg 117:108-116, Jan 1969

35. Iwatsuki S, Mikkelsen WP, Redeker AG, et al: Clinical comparison of the end-to-side and side-to-side portacaval shunt: Ten year follow-up. Ann Surg 178:65-69, 1973

36. Zuidema GD, Kirsh MM: Hepatic encephalopathy following portal decompression: Evaluation of end-to-side and side-to-side anastomosis. Amer Surg 31:567-569, 1965

37. Britton RC, Voorhees AB Jr, Price JB Jr: Perfusion of the liver following side-to-side portacaval shunt. Surgery 62:181-188, 1967

38. Mulder DG, Plested WG III, Hanafee WN, et al: Hepatic circulatory and functional alterations following side-to-side portacaval shunt. Surgery 59:923-931, 1966

39. LeVeen HH, Christoudias G, Ip M, et al: Peritoneo-venous shunting for ascites. Ann Surg 180:580-591, Oct 1974

40. Britton RC, Voorhees AB Jr, Price JB Jr: Selective portal decompression. Surgery 67:104-113, 1970

41. Bismuth H, Franco D, Hepp J: Portal-systemic shunt in hepatic cirrhosis: Does the type of shunt decisively influence the clinical result? Ann Surg 179:209-218, 1974

42. Malt RA, Szczerban J, Malt RB: Risks in therapeutic portacaval and splenorenal shunts. Ann Surg 184:279-288, 1976

43. Pliam MB, Adson MA, Foulk WT: Conventional splenorenal shunts: A reconsideration. Arch Surg 110:588-593, 1975

44. Mutchnick MG, Lerner E, Conn HO: Effect of portacaval anastomosis on hypersplenism in cirrhosis: A prospective controlled evaluation (Abstract). Gastroenterology 68:1070, 1975

45. Lord JW Jr, Rossi G, Daliana M, et al: Mesocaval shunt modified by the use of a Teflon prosthesis. Surg Gynecol Obstet 130:525-526, Mar 1970

46. Smith RB III, Warren WD, Salam AA, et al: Dacron interposition shunts for portal hypertension—An analysis of morbidity correlates. Ann Surg 192:9-17, Jul 1980

47. Drapanas T: Interposition mesocaval shunt for treatment of portal hypertension. Ann Surg 176:435-448, 1972

48. Drapanas T, LoCicero J III, Dowling JB: Hemodynamics of the interposition mesocaval shunt. Ann Surg 181:523-533, 1975

49. Rikkers LF, Rudman D, Galambos JT, et al: A randomized, controlled trial of the distal splenorenal shunt. Ann Surg 188: 271-282, Sep 1979

50. Reichle FA, Fahmy WF, Golsorkhi M: Prospective comparative clinical trial with distal splenorenal and mesocaval shunts. Am J Surg 137:13-21, 1979

51. Reichle FA, Owen OE: Hemodynamic patterns in human hepatic cirrhosis: A prospective randomized study of the hemodynamic sequelae of distal splenorenal (Warren) and mesocaval shunts. Ann Surg 190:523-534, 1979

52. Clatworthy H, Wall T, Watman RN: A new type of portal-to-systemic venous shunt for portal hypertension. Arch Surg 71: 588-599, 1955

53. Marion P: Les obstructions portales. Sem Hop Paris 29: 2781-2785, 1953

54. Voorhees AB Jr, Price JB Jr: Extrahepatic portal hypertension: A retrospective analysis of 127 cases and associated clinical implications. Arch Surg 108:338-341, 1974

55. Warren WD, Zeppa R, Fomon JJ: Selective trans-splenic decompression of gastroesophageal varices by distal splenorenal shunt. Ann Surg 166:437-455, 1967

56. Langer B, Rotstein LE, Stone RM, et al: A prospective randomized trial of the selective distal splenorenal shunt. Surg Gynecol Obstet 150:45-48, 1980

57. Resnick RH, Atterbury CE, Grace ND, et al: Distal splenorenal shunt (DSRS) vs. portalsystemic shunt (PSS): Current status of a controlled trial. Gastroenterology 77:A33, 1979

58. Busuttil RW, Brin B, Tompkins RK: Matched control study of distal splenorenal and portacaval shunts in the treatment of bleeding esophageal varices. Am J Surg 138:62-67, 1979

59. Zeppa R, Hensley GT, Levi JU, et al: The comparative survivals of alcoholics versus nonalcoholics after distal splenorenal shunt. Ann Surg 187:510-514, 1978

60. da Silva LC, Strauss E, Gayotto LCC: A randomized trial for the study of the elective surgical treatment of portal hypertension in mansonic schistosomiasis (Abstract). Gastroenterology 78:1321, 1980

61. Maillard JN, Flamant YM, Hay JM, et al: Selectivity of the distal splenorenal shunt. Surgery 86:663-671, Nov 1979

62. Vang J, Simert G, Hansson JA, et al: Results of a modified distal spleno-renal shunt for portal hypertension. Ann Surg 185: 224-228, 1977

63. Widrich WC, Robbins AH, Johnson WC, et al: Long-term follow-up of distal splenorenal shunts: Evaluation by arteriography, shuntography, transhepatic portal venography, and cinefluorography. Radiology 134:341-345, Feb 1980

64. Warren WD, Salam AA, Hutson D, et al: Selective distal splenorenal shunt: Technique and results of operation. Arch Surg 108:306-314, 1974

65. Inokuchi K, Kobayashi M, Ogawa Y, et al: Results of left gastric vena caval shunt for esophageal varices: Analysis of one hundred clinical cases. Surgery 78:628-636, 1975

66. Maillard JN, Rueff B, Prandi D, et al: Hepatic arterialization and portacaval shunt in hepatic cirrhosis: An assessment. Arch Surg 108:315-320, 1974

67. Adamsons RJ, Butt K, Iyer S, et al: Portacaval shunt with arterialization of the portal vein by means of a low flow arteriovenous fistula. Surg Gynecol Obstet 146:869-876, 1978

68. Cohn R, Herrod C: Some effects upon the liver of complete arterialization of its blood supply. Surgery 32:214-218, 1952

69. Wirthlin LS, Linton RR, Ellis DS: Transthoracoesophageal ligation of bleeding esophageal varices. Arch Surg 109:688-692, 1974

70. George P, Brown C, Ridgway G, et al: Emergency oesophageal transection in uncontrolled variceal haemorrhage. Br J Surg 60:635-640, 1973

71. Johnston GW: Simplified oesophageal transection for bleeding varices. Br Med J 1:1388-1391, 1978

72. Wexler MJ: Treatment of bleeding esophageal varices by transabdominal esophageal transection with the EEA stapling instrument. Surgery 88:406-416, 1980

73. Johnson G, Dart CH Jr, Peters RM, et al: Hemodynamic changes with cirrhosis of the liver: Control of arteriovenous shunts during operation for esophageal varices. Ann Surg 163: 692-703, 1966

74. Cooperman AM, Hermann RE: Ligation procedures in the management of portal hypertension. Surgery 81:382-385, 1977

75. Sugiura M, Futagawa S: A new technique for treating esophageal varices. J Thorac Cardiovasc Surg 66:677-685, Nov 1973

76. Sugiura M, Futagawa S: Further evaluation of the Sugiura procedure in the treatment of esophageal varices. Arch Surg 112: 1317-1321, 1977

77. Del Guercio LRM, Cohn JD, Kazaria KK, et al: A shunt equation for estimating the splenic component of portal hypertension. Am J Surg 135:70-75, 1978

78. Witte CL, Witte MH, Renert W, et al: Splenic artery ligation in selected patients with hepatic cirrhosis and Sprague-Dawley rats. Surg Gynecol Obstet 142:1-12, 1976

79. Smith GW: Splenectomy and coronary vein ligation for the control of bleeding esophageal varices. Am J Surg 119:122-131, 1970

80. Salam AA, Warren WD, Tyras DH: Splenic vein thrombosis: A diagnosable and curable form of portal hypertension. Surgery 74:961-972, 1973

81. Talma S: Chirurgische Oeffnung neuer Seitenbahnen für das Blut der Vena Porta. Berlin Klin Wochenschr 35:833-836, 1898

82. Hästbacka J: Thoracic transposition of the spleen for portal hypertension—A clinical and experimental investigation. Ann Chir Gynaecol Fenn 60(Suppl 176):1-77, 1971

83. Bengmark S, Börjesson B, Joelsson B, et al: Subcutaneous transposition of the spleen: A method for treatment of complications in portal hypertension? Ann Surg 189:75-83, Jan 1979

84. Campbell DP, Parker DE, Anagnostopoulos CE: Survival prediction in portacaval shunts: A computerized statistical analysis. Am J Surg 126:748-751, Dec 1973

85. Turcotte JG, Lambert MJ III: Variceal hemorrhage, hepatic cirrhosis, and portacaval shunts. Surgery 73:810-817, 1973

86. Cello JP, Deveney KE, Trunkey DD, et al: Factors influencing survival after therapeutic shunts: Results of a discriminant function and linear logistic regressions analysis. Am J Surg 141: 257-265, 1981

87. Mikkelsen WP: Therapeutic portacaval shunt: Preliminary data on controlled trial and morbid effects of acute hyaline necrosis. Arch Surg 108:302-305, 1974

88. Eckhauser FE, Appelman HD, O'Leary TJ, et al: Hepatic pathology as a determinant of prognosis after portal decompression. Am J Surg 139:105-112, 1980

89. Kanel GC, Kaplan MM, Zawacki JK, et al: Survival in patients with postnecrotic cirrhosis and Laennec's cirrhosis undergoing therapeutic portacaval shunt. Gastroenterology 73:679-683, 1977

90. Conn HO, Simpson JA: Excessive mortality associated with balloon tamponade of bleeding varices: A critical reappraisal. JAMA 202:587-591, 1967

91. Crafoord C, Frenckner P: New surgical treatment of varicose veins of the oesophagus. Acta Otolaryngol (Stockholm) 27: 422-429, 1939

92. Williams R, Clark AW, Macdougall BRD, et al: A prospective controlled trial of injection sclerotherapy in patients with cirrhosis and recent variceal hemorrhage. Gastroenterology 79: 1067, 1980

93. Terblanche J, Northover JMA, Bornman P, et al: A prospective controlled trial of sclerotherapy in the long term management of patients after esophageal variceal bleeding. Surg Gynecol Obstet 148:323-333, 1979

94. Lunderquist A, Vang J: Transhepatic catheterization and obliteration of the coronary vein in patients with portal hypertension and esophageal varices. N Engl J Med 291:646-649, Sep 26, 1974

95. Widrich WC, Robbins AH, Nabseth DC: Transhepatic embolization of varices. Cardiovasc Intervent Radiol 3:298-304, 1980

96. Pereiras R, Viamonte M Jr, Russell E, et al: New techniques for interruption of gastroesophageal venous blood flow. Radiology 124:313-323, 1977

97. Rueff B, Benhamou JP: Management of gastrointestinal bleeding in cirrhotic patients. Clin Gastroenterol 4:425-438, May 1975

98. Orloff MJ, Bell RH Jr, Hyde PV, et al: Long-term results of emergency portacaval shunt for bleeding esophageal varices in unselected patients with alcoholic cirrhosis. Ann Surg 192:325-338, 1980

99. Koransky JR, Galambos JT, Hersh T, et al: The mortality of bleeding esophageal varices in a private university hospital. Am J Surg 136:339-341, 1978

100. Malt RA, Abbott WM, Warshaw AL, et al: Randomized trial of emergency mesocaval and portacaval shunts for bleeding esophageal varices. Am J Surg 135:584-588, 1978

101. Viamonte M Jr, Warren WD, Fomon JJ, et al: Angiographic investigations in portal hypertension. Surg Gynecol Obstet 130:37-53, Jan 1970

102. Nordlinger BM, Nordlinger DF, Fulenwider JT, et al: Angiography in portal hypertension: Clinical significance in surgery. Am J Surg 139:132-141, Jan 1980

103. Rikkers LF, Miller F, Nelson JA, et al: Radiocolloid estimation of hepatic portal perfusion. J Surg Res 29:293-301, 1980

104. Reynolds TB: The role of hemodynamic measurements in portasystemic shunt surgery. Arch Surg 108:276-281, 1974

105. Rousselot LM, Ruzicka FF, Doehner GA: Portal venography via the portal and percutaneous routes: Anatomic and clinical studies. Surgery 34:557-569, 1953

106. Viallet A, Legare A, Lavole P: Hepatic and umbilicoportal catheterization in portal hypertension. Ann NY Acad Sci 170:177-192, 1970

107. Okuda K, Suzuki K, Musha H, et al: Percutaneous transhepatic catheterization of the portal vein for the study of portal hemodynamics and shunts: A preliminary report. Gastroenterology 73:279-284, 1977

108. Warren WD, Millikan WJ Jr, Smith RB III, et al: Noncirrhotic portal vein thrombosis: Physiology before and after shunts. Ann Surg 192:341-349, 1980

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Multiple Myeloma Complicating Gaucher's Disease

JOEL M. LAMON, MD: Although immunoglobulin abnormalities have been identified in patients with long-standing Gaucher's disease, reports of multiple myeloma complicating Gaucher's disease are infrequent. We present a case in which this association occurs. We will review selected problems of morphologically evaluating myeloma cells and with the treatment of multiple myeloma. We will also discuss previous experience regarding the association of these two disorders.

Case Presentation

WILLIAM MILLER, MD: The patient is a 66-year-old Jewish woman in whom Gaucher's disease was diagnosed at age 26 from tissue obtained at the time of a nonemergency cholecystectomy. When she was evaluated at the City of Hope Medical Center in 1977, a deficiency of the lysosomal enzyme glucocerebrosidase was documented in her leukocytes and platelets (see Table 1). Degenerative changes of the fifth lumbar vertebra were later discovered and a vertebral biopsy showed bone marrow replacement by typical Gaucher cells. A year later she began to have pain in her right leg. In addition to the collapse of the fifth lumbar vertebra, a large extradural defect at the body of L5 was seen on lumbar myelogram. An elective surgical procedure was done to excise the body of L5, decompress the dura and fuse the affected spine. Besides a large population of Gaucher cells, the vertebral body contained another population of atypical lymphocytoid cells. Serum protein electrophoresis showed a monoclonal spike in the gamma globulin region. Immunoelectrophoresis further characterized this as an IgG-kappa paraprotein. X-ray studies of the skull and long bones showed numerous lytic lesions suggesting features of multiple myeloma. Bone marrow specimens taken from the sternum and iliac crest showed both Gaucher cells and the atypical cells noted from the vertebral body, which were presumed to be plasma cells.

The patient was treated for ten months with melphalan and prednisone. No change in her paraprotein occurred and bone pain increased at sites other than the lumbar spine, especially the left leg. She received local radiation to sites of bone pain. Melphalan and prednisone were discontinued because of evidence of bone marrow depression. Aspiration of the bone marrow showed an increased fraction of Gaucher cells (Figure 1) but none of the previously seen myeloma cells. A recrudescence of bone pain, this time in her shoulders, right hip and leg, was partially relieved with local radiation, but residual pain in the right leg was severe enough to limit walking. The severe hip and leg pain and pancytopenia continued to be problems during a prolonged stay in hospital. The pancytopenia prevented aggressive chemotherapy. Radiation therapy was directed to foci of lytic bone lesions in an effort to relieve pain, but gave the patient only transient analgesia. A wide variety of analgesic agents were used to attempt to relieve her symptoms, with little success. This situation required that she be kept in

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ABBREVIATIONS USED IN TEXT

BCNU = carmustine
CML = chronic myelogenous leukemia
RER = rough endoplastic reticulum
VBAP = vincristine, BCNU, Adriamycin and prednisone
VBCMP = vincristine, BCNU, Cytoxan, melphalan and prednisone

hospital, with most of the therapeutic effort being directed towards relieving her pain. It is now more than 2½ years since the diagnosis of myeloma was made, and her clinical status has been unchanged with respect to pain control and bone marrow function.

Myeloma Associated With Gaucher's Disease

DR. LAMON: The prevalence of the adult nonneuropathic form of Gaucher's disease, an autosomal recessive disorder, has been estimated to be approximately 1 per 5,000. The prevalence of myeloma is 1 to 4 per 100,000. Simply combining these probability rates gives a frequency for the two diseases of less than 1 per million, assuming they are independent of one another. This does not include factors such as the advanced age of onset of multiple myeloma and the risk of premature death in Gaucher's disease. These factors should make an association of the two diseases even less probable. Therefore, the occurrence of the two diseases described by Dr. Miller in this patient is an unusual event. This is only the fourth reported case of multiple myeloma and Gaucher's disease occurring together.[1-3] However, these patients make up a subset of a larger number of patients in whom a variety of immunoproliferative disorders are found in association with chronic nonneuropathic Gaucher's disease.[4-14]

The presence of serum protein abnormalities in Gaucher's disease was first reported in 1950.[4] Four of five cases had an increase of gamma globulin, but no consistent pattern of abnormalities was observed. In a 1963 review of plasma cell myeloma, Osserman and Takatsuki[5] noted a monoclonal gammopathy without associated disease in a 68-year-old man with Gaucher's disease. Four years later in a review of Gaucher's disease, Chang-Lo and co-workers[6] reported 12 new cases. An increased number of plasma cells was seen in one patient, a 65-year-old woman; this case was unique among the 12 in that she was the only patient who noted bone pain. It is of interest that another of the 12 patients, a 61-year-old woman with lymphadenopathy, was also diagnosed as having chronic lymphocytic leukemia.[15] Pratt and co-workers[7] in 1968 reported their findings regarding the possible significance of serum protein abnormalities in Gaucher's disease. Sixteen patients with Gaucher's disease were categorized into the following three groups with respect to serum proteins: those with normal serum proteins, those with diffuse immunoglobulin elevation and those with homogeneous IgG

TABLE 1.—*Beta-glucosidase Activity in Various Cells From the Patient (μU per mg protein)**

Cell Type	*Patient*	*Normal Range*
Lymphocytes	10.0	40.2± 5.5
Monocytes	12.5	105.8±23.4
Granulocytes	2.2	15.7± 4.4
Platelets	7.9	25.9± 5.8

*Adapted from Beutler and co-workers.[27]

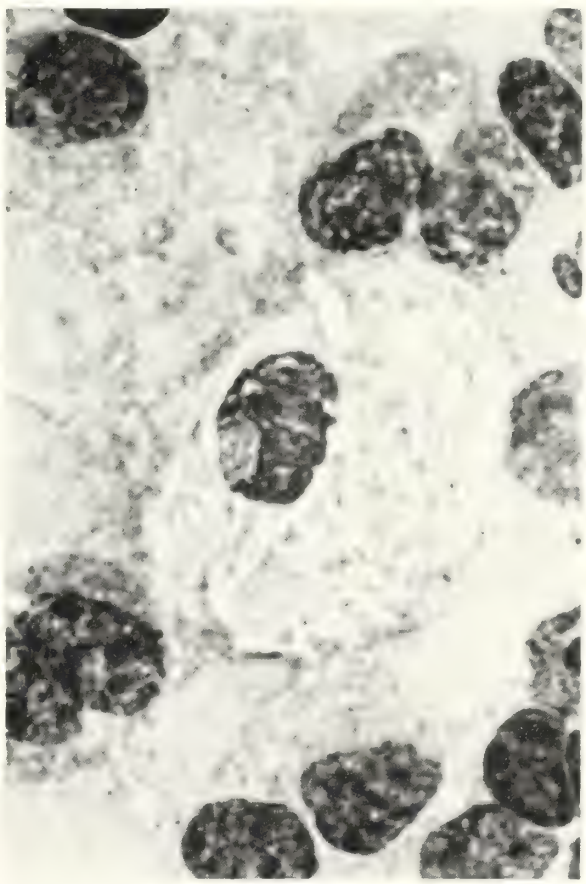

Figure 1.—Bone marrow aspirate from this patient. A Gaucher cell is in the center. It contains a single nucleus and abundant fibrillar structures. The cell is surrounded by numerous abnormal plasma cells. (Reduced from magnification ×1500.)

elevation. The first group contained six patients, all of whom were less than 50 years old. The second group was also comprised of six patients; these patients showed diffuse increases of one or more immunoglobulins. All of the patients in the third group (four) were older than 50; they had the highest levels of IgG (2,500 to 3,600 mg per dl) and the paraprotein was IgG kappa in each case. Each of the four patients had chronic infections or underlying liver disease to suggest a mechanism for hyperglobulinemia. Bone marrow specimens from this last group showed less than 5 percent plasmacytes in three patients and 18 percent in one patient. The only patient older than 50 in Pratt's series who did not show a monoclonal gammopathy had undergone a splenectomy. None of these four cases were considered to have multiple myeloma.

Two cases of monoclonal gammopathy in association with Gaucher's were reported by Wolf[9] in 1973. In one case multiple myeloma was the primary diagnosis and Gaucher's disease was substantiated only by morphology. As later pointed out by Scullin and associates,[16] this may be a spurious association in such a setting. The other case was a patient with long-standing Gaucher's disease with splenomegaly and anemia who also had a monoclonal gammopathy.

In another case report, a patient with long-standing Gaucher's disease with splenomegaly and documented low β-glucosidase activity in cultured fibroblasts was found to have a biclonal gammopathy.[10] Both IgG and IgA spikes were found, and by using fluorescent anti-IgG and anti-IgA two populations of plasma cells were identified. Following splenectomy the IgA concentration was reduced by 50 percent while the IgG level was not changed. This correlated with immunofluorescent studies of the spleen and marrow plasma cells. Both cell types were in the spleen, but the marrow plasma cells were exclusively IgG-staining cells. Immunofluorescent studies were also employed in the report by Turesson and Rausing[11] of a benign monoclonal gammopathy in a brother and sister, both with long-standing nonneuropathic Gaucher's disease. Both patients had splenomegaly and the M component was an IgA. The index case had IgA levels of 500 to 800 mg per dl, no osteolytic lesions and normal plasma cell numbers in repeated bone marrow aspirations. A subsequent splenectomy did not alter the M component of her protein electrophoresis. Immunofluorescent light-chain studies comparing the spleen and bone marrow indicated that the marrow IgA was monoclonal, while it was polyclonal in the spleen.

Figure 2.—Electron microscopic study of a Gaucher cell from splenic cord. The large cell consists mostly of cytoplasm with a small peripheral nucleus. The cytoplasm contains an abundance of irregular fibrillar structures with a twisted appearance and a few granules. (Reduced from magnification ×9000.)

Besides true myeloma and benign gammopathies, reports of Gaucher's disease in association with abnormal proteins contribute to speculation regarding a possible etiologic relationship of the underlying Gaucher's disease with the development of an immunoproliferative disorder. Benjamin and co-workers[12] described cryoglobulinemia in a 70-year-old woman with Gaucher's disease. The cryoglobulin was a mixture of a monoclonal IgM kappa and polyclonal IgG. Dikman and colleagues[13] reported the presence of systemic amyloidosis, light chain in the urine and marrow plasmacytosis in a 48-year-old man with Gaucher's disease. The patient had splenomegaly with significant amyloid involvement of that organ as well as other organs. A moderate increase in marrow plasma cells was described without further quantitation. Serum concentration of IgG was low, while IgA and IgM were normal.

This discussion would be incomplete without

briefly considering the occurrence of pseudo-Gaucher cells with malignant hematologic changes. The reports by Scullin[16] regarding multiple myeloma and several others regarding the phenomena in chronic myelogenous leukemia (CML) suggest that the increased cell turnover can saturate available metabolic capacity for membrane protein turnover.[17-20] It is of interest that the electron micrographs from this patient demonstrate inclusions that are characteristic of Gaucher and non-CML cells as noted by Lee[20] (Figure 2). Dr. Tavassoli will discuss the morphologic features of Gaucher's disease.

Histopathology of Gaucher's Disease and Myeloma

MEHDI TAVASSOLI, MD:* Gaucher's disease can involve all organs, but the liver, spleen and the bone marrow are major sites of cell accumulation. The brain is not involved in the chronic non-neuropathic form that we are discussing. Myeloma is primarily a disease of the bone marrow and only rarely involves spleen. The total pathology of Gaucher's disease complicated by myeloma is, of course, the sum of the total pathology of the two entities. Both are infiltrative diseases, one being neoplastic and the other nonneoplastic. In both situations the infiltration is patchy; hence, the density of the infiltration can vary considerably from one biopsy sample to the next, as well as the histopathology from any one bone marrow sample. Because of their infiltrative nature, both diseases can alter the marrow architecture of the host tissue. The bone marrow may demonstrate a myelophthisis with leukoerythroblastosis.[21] This picture is not common, however.

Histopathology of Gaucher's Disease

The pathologic hallmark of Gaucher's disease is the Gaucher cell.[22-24] This is a morphologically characteristic macrophage that stores membrane-derived glucocerebroside that cannot be broken down because of the inherited glucocerebrosidase deficiency. The cell can be recognized in the smear and the biopsy section. It is 40 to 80 μm in diameter and has ample cytoplasm and a relatively small single nucleus or multiple nuclei (Figure 1). The cytoplasm is faintly eosinophilic and contains weblike fibrillar structures, most clearly recognized by phase microscopy but also in the stained smear. This fibrillar appearance is distinctly different from the foamy appearance of cells in Niemann-Pick disease, a sphingomyelin storage disease. Cytochemically, Gaucher cell reacts to periodic acid-Schiff (PAS) (because of the carbohydrate moiety of the stored substance) but does not react to Sudan black B. It reacts strongly to acid phosphatase, which may also be elevated in the serum. (This is a low molecular weight enzyme distinctive from other acid phosphatases.) The cell also contains large amounts of stainable iron.

By electron microscopy, the fibrillar structures of the cytoplasm are 15 to 40 nm in thickness and are interspersed with characteristic lipid granules (Figure 2). The fibrillar structures have a characteristic twisted appearance and are wrapped in a membrane. Lipid granules contain glucocerebroside that accumulates as the metabolism of cell membranes is impaired at the catabolic step that metabolizes the monohexose ceramide. Myelin figures, common in Niemann-Pick disease, are not seen in the Gaucher cell. This is attributed to low water solubility of glucocerebrosidase. In the spleen, Gaucher cells infiltrate the cordal areas. In the bone marrow, the infiltration is in the hemopoietic compartment.

Histopathology of Myeloma[25,26]

While the infiltration of the bone marrow by the myeloma cell is in the hemopoietic compartment, in plasma cell leukemia the cells may also be present in the vascular element. In those rare cases where the spleen is also involved, the marginal zone appears to be the primary site of involvement. The hallmark of myeloma cells is the nuclear-cytoplasmic dissociation. An immature nucleus, often containing a large "punched-out" nucleolus, is surrounded by mature metabolically active cytoplasm. Multiple nuclei are frequent, and the strong basophilia in the Wright-Giemsa preparation is a consequence of the large concentration of rough endoplasmic reticulum (RER). Lamellar, tubular or vesicular cytoplasmic patterns occur as negative images in the intensely basophilic cytoplasm. These areas may be distended with a flocculent material that on high resolution studies contains filaments, crystals or dense precipitates (spheroid bodies). Intracytoplasmic and even rarely intranuclear inclusions are seen. These are usually profiles of RER distended with myeloma protein and may fill the

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entire cytoplasm, giving the cell a foamy appearance (foam cells). When the carbohydrate component of the myeloma cells is high, as in IgA myeloma, they may show intense PAS-positivity and are generally known as flame cells.

The presence of monoclonal serum protein, urine light-chain excretion or lytic bone lesions that are unusual for Gaucher's disease may raise a clinical suspicion that multiple myeloma may be complicating Gaucher's disease. Bone marrow examination or biopsy of a lytic lesion are the most direct approaches to diagnosis. A biopsy of a myeloma-induced lesion should establish the diagnosis. However, the fact that both diseases cause diffuse marrow infiltration may lead to an interpretation error in random aspirates and biopsies. The morphologic features discussed above may help to distinguish the presence of both proliferative entities.

Management of Multiple Myeloma

ROBERT LONGMIRE, MD: An untreated patient with myeloma has a life span of a year or slightly less, but the usual median survival of patients given chemotherapy is in the range of 20 to 36 months with the possibility of 20 percent of patients surviving five years. The presence of Gaucher's disease associated with multiple myeloma presents an interesting chemotherapeutic problem of exposing an individual with impaired marrow reserve, as a result of Gaucher cell and plasma cell infiltration, to hematologically toxic agents. Gaucher's disease patients in this position, as in the present case and those discussed by Dr. Lamon from the literature, are further limited in their hematologic and immunologic competence by hypersplenism. One might expect an anemia associated with untreated multiple myeloma to be relieved by the successful application of chemotherapy to the plasma cell infiltrations. However, that may not be a reasonable expectation when Gaucher's disease is also present, and in fact was not achieved in the complex problem presented in this case. I shall attempt to consider this difficult situation in the context of the usual approach to treatment of multiple myeloma.

In the treatment of multiple myeloma, partial responses are often easily obtained with various chemotherapeutic modalities. These result in prolonged survival, but relapse is the rule. The standard mode of therapy consists of melphalan and prednisone, which are given in various schedules, the most usual being a five-day course of the two agents every four to six weeks. For those patients responding to melphalan-prednisone, approximately 70 percent to 90 percent reduction in total myeloma burden may be expected after six to nine months of treatment. Myeloma cells exhibit growth characteristics described by the Gompertzian growth curve. That is, as the total plasma cell burden is diminished the growth fraction of the tumor mass increases. These two factors, cell death from treatment and an increased growth fraction of the remaining cells, should result in a plateau phase with respect to the tumor mass. In this setting an eventual relapse is expected from the emergence of a biochemically or kinetically resistant clone. Response may be judged at regular intervals by the size of the M component or by total proteinuria. Normalization of immunoglobulins, correction of anemia, recalcification of bone lesions and clinical improvement are also useful correlations of successful treatment. Bone marrow examination may be helpful, but myeloma can have a spotty distribution and false-negative information may occur from sampling errors. In those myelomas secreting only light chains, evaluation of a 24-hour urine specimen for creatinine clearance becomes the major measurement to follow in judging response. The nonsecreting myeloma is more difficult to evaluate. The labeling index with tritiated thymidine, when available, is a useful criterion of response, and it may be the only objective measurement of response other than the clinical data mentioned above.

Melphalan and prednisone will produce an approximately 60 percent response rate. For those patients achieving complete response it has not proved useful to continue maintenance therapy. Besides the risk of acute leukemia or sideroblastic anemia from prolonged exposure to melphalan, no prolongation of survival has been proved with maintenance therapy. A substantial number of patients who relapse after a judged complete remission may again respond to the original induction program. Those patients who fail to respond to the initial therapy or who relapse while on therapy may respond to combinations of vincristine sulphate, BCNU (carmustine), doxorubicin hydrochloride (Adriamycin) or cyclophosphamide (Cytoxan). Two commonly used programs at the present time are (1) vincristine, BCNU, Adriamycin and prednisone (VBAP), or (2) vincristine, BCNU, Cytoxan, melphalan and prednisone (VBCMP). When stability but no im-

provement is detected, consideration should be given to a change of agents, though retaining vincristine. In this situation, with successful reduction of total tumor mass and subsequent increased growth fraction of the remaining myeloma cells, a cycle-specific agent such as vincristine would be most effective.

The complications of multiple myeloma must be kept constantly in mind and may be the factors that cause a patient to seek medical care. These include anemia, hemorrhage, hypercalcemia, hyperviscosity and renal failure. Anemia is a distressing complication of myeloma that frequently necessitates transfusion, especially during the early phases of treatment when it may be the presenting complaint. Although controversial, the use of testosterone derivatives may be helpful in promoting appetite, strength and erythroid stimulation. Thrombocytopenia is often part of the initial clinical picture or it may occur during treatment. It may be necessary to administer platelet transfusions as a supportive measure during induction chemotherapy or at some time during the course of the myeloma. In addition to an enhanced risk of bleeding from reduced platelet number, adsorption of immunoglobulins to platelet surfaces may impair platelet function and thus contribute to a hemorrhagic tendency. Hypercalcemia is a frequently encountered complication and is not a contraindication for chemotherapy. In fact, effective chemotherapy may contribute to an improvement. Although a complete discussion of life-threatening hypercalcemia is not intended, the use of mithramycin should be noted. This agent may depress bone marrow function and result in a limitation of maximum chemotherapy for the myeloma. Hyperviscosity syndromes are best treated by treating the myeloma. Plasmapheresis may be necessary if the risk of sludging or gel formation in the vessels is high. Acute and chronic renal failure are potential complications, and hemodialysis may yield prolonged symptom-free survival.

A further complication is the appearance of plasmacytomas. Their occurrence with erosion and potential fracture is an indication for radiation therapy. Extradural cord compression should be managed with radiation therapy; however, if a progressive deficit in neurological function occurs, surgical decompression may be necessary. This complication was, in fact, an initial problem in this case. Plasmacytomas may occur while the patient is in apparent remission and may herald an exacerbation of the disease or the recrudescence of a rapidly expanding clone of cells.

Gaucher's Disease

ERNEST BEUTLER, MD: When Phillippe Gaucher first described the disease that now bears his name, he found the spleen and bone marrow to be infiltrated with large abnormal-appearing cells. It is no wonder that in 1882 he considered the disorder to be neoplastic in nature with "malignant" cells destroying the tissues they invaded. With the recognition that these infiltrated organs contained vast amounts of cerebrosides, Gaucher's disease was identified as one of a heterogeneous group of "storage" disorders. Even when the lipid was recognized as glucocerebroside, the explanation for its accumulation remained unknown: the theories of overproduction and abnormal degradation each had their exponents.

In the past two decades, the storage disorders have become much better understood. They are due to deficiencies of metabolic enzymes—enzymes that cleave complex molecules into ever simpler compounds that eventually leave the cell and reenter the metabolic stream. Gaucher's disease is due to deficiency of a lysosomal enzyme, glucocerebrosidase. Glucocerebroside is a common end product in the degradation of membrane lipids, both globosides and gangliosides. Consisting of ceramide (a sphingosine-fatty acid complex) with β-glucose bound to the sphingosine, this highly insoluble substance is normally cleaved to glucose and ceramide by glucocerebrosidase. A deficiency of glucocerebrosidase allows the glucocerebroside to accumulate in macrophages. As a reaction to the retained glycolipid, the cells enlarge and occupy space that should be devoted to healthy cells of liver, bone marrow or spleen. In the rare infantile form of this disorder, the central nervous system is affected as well, but in the more common adult type of Gaucher's disease, a disorder found most commonly among Jews of Eastern European origin, bone lesions and hematologic involvement are most common. Our patient exhibits many of the classical manifestations of this disease.

It is evident that despite a steady influx of substrate from normal cell turnover into the degradative pathway, a linear progression of organo-

megaly does not occur. Apparently a plateau of glucocerebrosidase accumulation is reached, but the mechanism for this is not understood.

It is not known whether a chronic antigenic stimulus is present in Gaucher's disease. Thus, the pathogenetic basis of the development of immunoglobulin abnormalities and neoplasia in patients with Gaucher's disease remains a mystery.

Summary

DR. LAMON: The apparent predisposition of patients with Gaucher's disease to the development of paraproteinemias and even multiple myeloma in a few instances is unexplained. The past two decades have witnessed great strides in the understanding of both diseases, yet their interaction, both etiologically with regard to myeloma and immunologically with respect to a possible antigenic stimulus in Gaucher's disease, is explained only by untested hypotheses.

Galactocerebroside has been suggested as a potential factor in the association of the diseases, because it is the only product of the glucocerebrosidase deficiency known to be antigenic. Nonetheless, there is no evidence that monospecific antibody to this antigen has occurred with the development of multiple myeloma. Another possible explanation is that there is a familial predisposition to immunologic abnormalities, perhaps a linkage of the glucocerebrosidase locus to a human equivalent of the immune response gene. However, epidemiologic clues such as the presence of myeloma or nonspecific immunologic abnormalities in family members of Gaucher's disease patients do not exist. A more complex association with glucocerebrosidase deficiency and perhaps a subtle variation in the immune response cannot be excluded by the absence of epidemiologic data in these healthy family members.

REFERENCES

1. Pinkhas J, Djaldetti M, Yaron M: Coincidence of multiple myeloma with Gaucher's disease. Israel J Med Sci 1:537-540, Jul 1965

2. Benjamin D, Joshua H, Djaldetti M, et al: Nonsecretory IgD-kappa multiple myeloma in a patient with Gaucher's disease. Scand J Haematol 22:179-184, 1979

3. Ruestow PC, Levinson DJ, Catchatourian R, et al: Coexistence of IgA myeloma and Gaucher's disease. Arch Intern Med 140:1115-1116, 1980

4. Goldfarb AR, Atlas DH, Gaberman P: Electrophoretic studies in Gaucher's disease. Am J Pathol 20:963-965, 1950

5. Osserman EF, Takatsuki K: Plasma cell myeloma: Gamma globulin synthesis and structure. Medicine 42:357-384, 1963

6. Chang-Lo M, Yam LT, Rubenstone AI: Gaucher's disease—Review of the literature and report of twelve new cases. Amer J Med Sci 254:303-315, Sep 1967

7. Pratt PW, Estren S, Kochwa S: Immunoglobulin abnormalities in Gaucher's disease—Report of 16 cases. Blood 31:633-640, 1968

8. Blattner RJ: Gaucher's disease: Abnormalities in immunoglobulins. J Pediatr 73:626-628, 1968

9. Wolf P: Monoclonal gammopathy in Gaucher's disease. Lab Med 4:28-29, 1973

10. MacDonald M, McCathie M, Faed MJW, et al: Gaucher's disease with biclonal gammopathy. J Clin Pathol 28:757, 1975

11. Turesson I, Rausing A: Gaucher's disease and benign monoclonal gammopathy. Acta Med Scand 197:507-512, 1975

12. Benjamin D, Douer D, Pick AI, et al: Peripheral cryoglobulinemic neuropathy in a patient with Gaucher's disease. Acta Haematol 60:117-121, 1978

13. Dikman SH, Goldstein M, Kahn T, et al: Amyloidosis: An unusual complication of Gaucher's disease. Arch Pathol Lab Med 102:460-462, 1978

14. Shoenfeld Y, Berliner S, Pinkhas J, et al: The association of Gaucher's disease and dysproteinemias. Acta Haemat 64:241-243, 1980

15. Chang-Lo M, Yam LT, Rubenstone AI, et al: Gaucher's disease associated with chronic lymphocytic leukemia, gout and carcinoma. J Pathol 116:203-207, 1970

16. Scullin DC, Shelbourne JD, Cohen J: Pseudo-Gaucher cells in multiple myeloma. Am J Med 67:347-352, 1979

17. Albrecht M: "Gaucher-Zellen" bei chronisch myeloischer Leukamie. Blut 13:169-179, Jun 1966

18. Kattlove HE, Williams JC, Gaynor E, et al: Gaucher cells in chronic myelocytic leukemia: An acquired abnormality. Blood 33:379-390, Feb 1969

19. Gerdes J, Marathe RL, Bloodworth JM, et al: Gaucher cells in chronic granulocytic leukemia. Arch Path (Chicago) 88:194-198, Aug 1969

20. Lee RI, Ellis LD: The storage cells of chronic myelogenous leukemia. Lab Invest 24:261-264, Apr 1971

21. Tavassoli M: Erythroblastemia. West J Med 122:194-198, 1975

22. DeMarsh QB, Kautz J: The submicroscopic morphology of Gaucher cells. Blood 12:324-335, 1957

23. Pennelli N, Scaravilli F, Zacchello F: The morphogenesis of Gaucher cells investigated by electron microscopy. Blood 34:331-347, Sep 1969

24. Lee RE, Balcerzak SP, Westerman MP: Gaucher's disease—A morphologic study and measurements of iron metabolism. Amer J Med 42:891-898, Jun 1967

25. Zucker-Franklin D: Multiple myeloma—II. Structural features of cells associated with the paraproteinemias. Seminars Hemat 1:165-198, Apr 1964

26. Brecher G, Tanaka Y, Malmgren RA, et al: Morphology and protein synthesis in multiple myeloma and macroglobulinemia. Ann NY Acad Sci 113:642-653, 1964

27. Beutler ER, Kuhl W, Matsumoto F, et al: Acid hydrolases in leukocytes and platelets of normal subjects and in patients with Gaucher's and Fabry's disease. J Exp Med 143:975-980, Apr 1, 1976

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Asthma, Sulfur Dioxide and the Clean Air Act

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *This Medical Staff Conference will be concerned with our chemical environment and the public policies designed to control that environment in a manner consistent with human health. The topic will be "Asthma, Sulfur Dioxide and the Clean Air Act." Dr. Homer Boushey will give the presentation.*

DR. BOUSHEY:† In my discussion I shall relate the findings of our laboratory on the effects of sulfur dioxide (SO_2) in patients with asthma, first to theories about the mechanisms of bronchial hyperreactivity, an abnormality that may be fundamental to the pathogenesis of asthma and then to questions of national policy on air quality. I plan also to review briefly some of the epidemiologic data that suggest a relationship between levels of sulfur dioxide and particulates in the air and respiratory disease, and finally to explain the controversy over how the Clean Air Act of 1970 should be amended before it is reauthorized.

Historical Background

Historically, the clearest evidence for a relationship between levels of sulfur dioxide and particulates and death was made apparent by a number of acute air pollution crises in which meteorologic conditions resulted in stagnation of air and pronounced increases in the level of air pollutants. The first of these to be recognized occurred in the Meuse Valley in Belgium in the mid-1930's.[1] Another occurred in this country in Donora, Pennsylvania, in 1948,[2] but the most dramatic of the acute episodes occurred in London in December 1952.[3] An unusually dense smog rich in sulfur dioxide and particulates enveloped virtually the whole of Greater London from Friday through Tuesday morning. Over the days of the smog and the two weeks thereafter, the death rate in Greater London achieved a level that had rarely been exceeded in the previous 100 years, for example, at the height of the cholera epidemic of 1854, and of the influenza epidemic of 1918-1919. Comparison of mortality during the crisis with mortality in the previous weeks and with the same period in the previous year showed that there were between 4,000 and 8,000 more deaths than usual in London over 11 days. Most of these deaths were attributed to respiratory diseases—pneumonia, bronchitis, lung cancer, asthma or "other respiratory diseases." The increase in mortality was greatest in infants and elderly people,

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ABBREVIATIONS USED IN TEXT

EPA = Environmental Protection Agency
ppm = parts per million

but mortality was also increased in young adults and adolescents.

The observed relationship between levels of sulfur dioxide and particulates and excess mortality during acute air pollution crises led to investigations of the relationship between daily mortality and levels of these pollutants. Studies from many different countries have shown a similar trend of higher mortality on days with greater air pollution. One study in New York, for example, correlated deaths from all reported causes on a daily basis from 1962 through 1966 with the levels of sulfur dioxide and particulates measured in Upper Manhattan.[4] After death rates were adjusted for seasonal cycles, temperature, influenza epidemics, holidays and so forth, they significantly correlated with levels of sulfur dioxide. Mortality was 2 percent greater than predicted on days when sulfur dioxide exceeded 0.19 parts per million (ppm), and was 1.5 percent less than predicted on days when sulfur dioxide was less than 0.01 ppm. These data do not specifically incriminate sulfur dioxide as responsible for the increase in mortality, for sulfur dioxide levels are usually paralleled by levels of particulates. It is possible that particulate matter or some other copollutant, rather than sulfur dioxide itself, is responsible for the differences in mortality.

Other epidemiologic studies have shown that levels of sulfur dioxide and particulates also correlate with the prevalence of chronic respiratory disease. The symptoms of persistent cough and sputum production in adults and the incidence of premature retirement or death from bronchitis have been found to be greater in areas with higher levels of sulfur dioxide and particulates, even when differences in social class and smoking habits are taken into account.[5] These differences are widened between smokers and nonsmokers as air pollution increases, suggesting some synergism between air pollution and cigarette smoking in producing chronic obstructive pulmonary disease. The findings of studies in children are similar; the incidence of infections of the lower respiratory tract correlates with residence in areas of greater air pollution.[6] This may be particularly important, for other epidemiologic studies show that the incidence of obstructive ventilatory defects in adults correlates with the history of lower respiratory tract infections in childhood.

Epidemiologists appear to have been quicker than clinical physiologists or toxicologists in recognizing that people with asthma may represent a subsegment of the population particularly sensitive to sulfur dioxide. In the episode in Donora, for example, 88 percent of the people with asthma complained of marked respiratory symptoms; only 43 percent of the general population had similar complaints. Subsequent studies have shown that the frequency of emergency room visits for asthmatic complaints correlates with atmospheric levels of sulfur dioxide.[7] Zeidberg and co-workers[8] similarly found a direct correlation between the severity of asthmatic symptoms as inferred from diaries kept by asthmatic patients and the atmospheric levels of sulfur dioxide. This finding is remarkable because the levels of sulfur dioxide in Nashville, where the study was done, were lower than in larger industrial cities of the Northeast and Midwest of this country.

Despite these provocative epidemiologic studies, one must be cautious in attributing worsening of asthmatic symptoms to levels of a particular pollutant. Not only is sulfur dioxide ordinarily present with other pollutants, especially particulates, but other atmospheric variables such as air temperature or humidity might also have interacted with sulfur dioxide or a copollutant in producing the symptoms. Another problem is that asthmatic symptoms may be provoked by a wide variety of agents and events. The amount of dust or pollens in the air might have increased, for example, during the thermal inversions that resulted in higher levels of sulfur dioxide. The epidemiologic studies can therefore provide suggestive circumstantial evidence but do not pinpoint sulfur dioxide as the cause of the worsening of asthmatic symptoms. For this reason, laboratory studies of the effects of a single pollutant on pulmonary function are important. For sulfur dioxide, such studies showed little response in healthy people exposed to concentrations below 5 ppm, a high level of sulfur dioxide. Frank and associates[9] exposed 11 healthy adults to 1, 5 and 13 ppm of sulfur dioxide and found no change in the mean value for airway resistance after exposure to 1 ppm, a level infrequently exceeded in most American cities. They found significant increases in resistance on exposure to 5 and 13 ppm, but these levels are achieved only in certain

occupational settings, not in the general atmosphere. Frank and co-workers[9] did find, however, that one of their subjects had considerable bronchospasm on inhaling 1 ppm, and they remarked that this person's history of wheezing with viral infections suggested that he might have had an asthmatic predisposition. Their study is typical of many studies done in the 1960's; that is, in groups of healthy adult volunteers who were exposed to sulfur dioxide, no changes in maximal expiratory flow or in airway resistance were found in the group as a whole with exposure to levels of sulfur dioxide below 5 ppm. In some people, however, many of whom were reported to have occasional asthmatic symptoms, substantial responses occurred with exposure to much lower levels (such as 1 ppm). Despite these observations, the first study of a group of asthmatic subjects was not undertaken until 1980 when Sheppard, Wong, Uehara and others in our laboratory[10] investigated the effects of SO_2 in people with asthma.

Effects on Persons With Asthma

Our work was not provoked so much by curiosity over the disparity between the results of the epidemiologic studies, which suggested a strong relationship between low levels of sulfur dioxide and asthmatic symptoms, and the results of controlled exposure studies, which showed no effect of levels below 5 ppm except in an occasional and possibly random individual. Rather, our investigation was spurred by our interest in the mechanism of bronchial hyperreactivity. It has long been known that patients with asthma will have intense, symptomatic bronchospasm on inhaling levels of histamine or methacholine so small as to cause no measurable effect in normal people. This abnormal responsiveness of the airways is referred to as bronchial hyperreactivity; it is ubiquitous in people with asthma and the degree of bronchial hyperreactivity correlates with the clinical severity of asthma as estimated by symptom scores or medication requirements. Furthermore, the events that increase bronchial reactivity, such as viral infections and exposure to oxidizing pollutants, also increase the clinical severity of asthma. There is now a widespread consensus among investigators that bronchial hyperreactivity is somehow fundamental to the pathogenesis of asthma; that is, asthma may require not just the release of the chemical mediators of anaphylaxis, but also an exaggeration of the responsiveness of the pulmonary system to their effects.[11] Despite the consensus about the importance of bronchial hyperreactivity, there is little agreement as to its underlying mechanisms. The hypothesis we favor is that bronchial hyperreactivity is due to an exaggeration of reflex responsiveness to inhaled materials (Figure 1).

Evidence supporting this hypothesis was initially provided by studies in dogs, in which cutting the vagus nerves greatly reduced the response to inhaled or injected histamine.[12] It was later shown that in people with asthma or chronic bronchitis, pretreatment with atropine sulfate (a postganglionic cholinergic antagonist that has no effect on the response of smooth muscle to histamine in vitro) blocked the response to subsequent inhalation of histamine.[13] This finding suggests that the exaggerated response to histamine associated with asthma is mediated through parasympathetic pathways, but it does not identify the site of altered function within the pathway. Holtzman

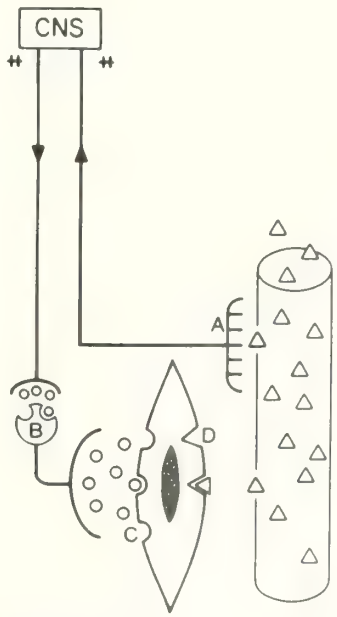

Figure 1.—Conceptual model of mechanisms of response to inhaled irritants. The airway is represented by a hollow cylinder with branching vagal sensory endings (A) lying adjacent to the lumen. Afferent pathways in the vagus nerves travel to the central nervous system (CNS); efferent pathways from the CNS travel to efferent ganglia (B). Postganglionic fibers release acetylcholine (o), which binds to muscarinic receptors (C) on airway smooth muscle. Inhaled histamine (Δ) normally causes bronchoconstriction by two mechanisms: it diffuses across the airway epithelium and binds to histamine receptors (D) on smooth muscle, provoking contraction; histamine also stimulates vagal sensory endings causing reflex release of acetylcholine at the postganglionic nerve endings and further provoking muscle contraction. (Adapted from Holtzman et al.[14])

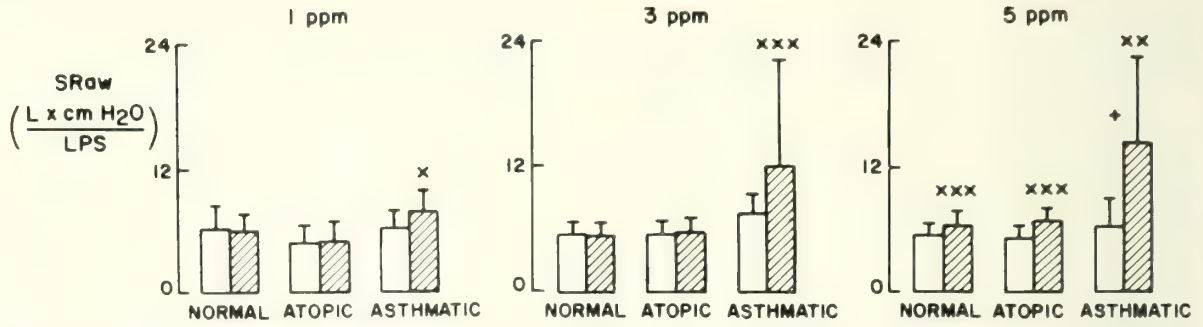

Figure 2.—Specific airway resistance (SRaw) after 5 min of breathing filtered air (□) and during the last 5 min of exposure (▨) to 1, 3 and 5 ppm of sulfur dioxide in normal, atopic and asthmatic subjects. Data are mean ± standard deviation; n = 7 except for asthmatic subjects breathing 5 ppm; in this group, n = 6. x, xx, xxx significantly different from value after exposure to air—$P<0.05$, 0.025, and 0.01, respectively; increase in SRaw significantly greater in asthmatic group—$P<0.005$. Units L × cm H_2O/LPS refers to liters of lung volume times airway resistance (cm H_2O/liters per second). (Reproduced with permission from Sheppard et al.[10])

and co-workers[14] have since found that pretreatment with aerosolized hexamethonium, a ganglion-blocking agent, also blocked the response to inhaled histamine. Hexamethonium did not, however, alter the response to inhaled methacholine, a drug that acts directly at muscarinic receptor sites. This finding suggests that bronchial hyperreactivity is due to a difference in activity distal to the ganglion, possibly in the number or binding affinity of muscarinic receptors on bronchial smooth muscle. If this hypothesis is correct, any agent that acts uniquely through reflex pathways should cause exaggerated bronchoconstriction in people with bronchial hyperreactivity. Sulfur dioxide appears to be such an agent. Nadel and associates[15] have shown in cats that the insufflation of sulfur dioxide into the isolated upper airway caused constriction of both upper and lower airways; the converse was also true: insufflation of sulfur dioxide into the lower airways caused upper airway contraction. These responses were further shown to depend on innervation of the larynx and tracheobronchial tree; sulfur dioxide had little direct effect on smooth muscle.

As a test of our hypothesis on the mechanism underlying bronchial hyperreactivity, we predicted that people with asthma should be abnormally sensitive to sulfur dioxide. Accordingly, we studied seven healthy people, seven people with atopic disease—usually allergic rhinitis, but without asthma—and seven with mild asthma.[10] Each person was exposed for ten minutes to 1, 3, or 5 ppm of sulfur dioxide while breathing through a mouthpiece. In the asthmatic persons specific airway resistance increased significantly after inhaling each level of sulfur dioxide, and the magnitude of the response was related to the concentration inhaled (Figure 2). The response of the asthmatic persons was significantly greater than those of the atopic and healthy control subjects. Two of the people with asthma complained of wheezing and shortness of breath on inhaling 1 ppm; four of six complained of wheezing and shortness of breath on inhaling 5 ppm. In some subjects, the response was dramatic even at 3 ppm (Figure 3). Pretreatment with aerosolized atropine sulfate blocked the response to sulfur dioxide in all subjects. Thus, our study showed that people with asthma responded to lower levels of sulfur dioxide and with greater bronchoconstriction than people without asthma.

Because atmospheric levels of sulfur dioxide rarely exceed 1 ppm in American cities, the relevance of our findings to normal living conditions

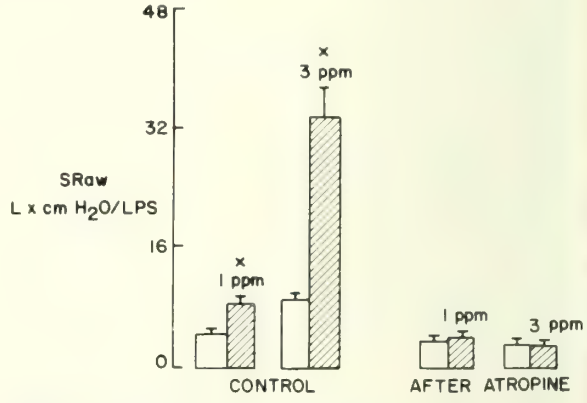

Figure 3.—Specific airway resistance (SRaw) after 5 min of breathing filtered air (□) and during the last 5 min of exposure to 1 and 3 ppm of sulfur dioxide (▨) in the control state and after treatment with atropine sulfate in one asthmatic subject. Data are mean ± SD; x significantly different from value after exposure to air—$P<0.0005$. Units L × cm H_2O/LPS refers to liters of lung volume times airway resistance (cm H_2O/liters per second). (Reproduced with permission from Sheppard et al.[10])

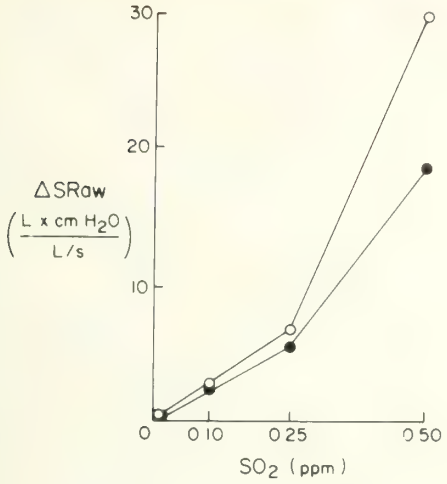

Figure 4.—Dose-response to sulfur dioxide (SO_2) inhaled during exercise in two subjects (● and o). The ΔSRaw is the difference between baseline specific airway resistance and specific airway resistance after inhalation of SO_2. (Reproduced with permission from Sheppard et al.[16])

could be questioned, but they are clearly relevant to the work place, where the permitted level of sulfur dioxide is 5 ppm in a time-weighted average over eight hours. Sulfur dioxide levels are therefore permitted to be much higher than 5 ppm for short periods of time without violating the Occupational Safety and Health Administration (OSHA) standard.

The finding that people with asthma also develop bronchoconstriction on inhaling lower concentrations of SO_2 was made by Sheppard and co-workers[16] who remarked that in the first study, all subjects were exposed to SO_2 while seated and at rest. Sulfur dioxide is a highly soluble gas and is well absorbed by the mucosa of upper airways. Only a small proportion of the concentrations entering the mouth travels below the larynx. Sheppard predicted that with the increase in both inspiratory flow and volume required for exercise, a greater proportion of inhaled SO_2 would reach the larynx and tracheobronchial tree, and more pronounced responses would result. Sheppard's study of the interaction of exercise and sulfur dioxide in seven people with very mild asthma confirmed this prediction.[16] Neither inhalation of 0.5 ppm of sulfur dioxide at rest, nor moderate exercise (400 kilopond-meters per minute) while breathing humidified filtered air caused an increase in specific resistance. At the same level of exercise while breathing 0.5 ppm of sulfur dioxide, however, specific airway resistance increased strikingly, and several subjects complained of chest tightness and shortness of breath. When the same people were challenged with 0.25 ppm of sulfur dioxide, a small but statistically significant increase in specific resistance persisted. In the two most sensitive persons, inhalation of as little as 0.1 ppm of SO_2 during moderate exercise caused a small but significant increase in specific airway resistance (Figure 4). This demonstrates that very low levels of sulfur dioxide inhaled during exercise can cause bronchospasm in people with asthma.

Our findings that the airways of people with asthma are sensitive to sulfur dioxide and that exercise potentiates the responsiveness have been confirmed by investigators at the University of Washington using slightly different methods. Koenig and co-workers[17] have reported that adolescents with asthma and children with hay fever are more sensitive to sulfur dioxide, and that this sensitivity is potentiated by exercise.

With respect to our understanding of the mechanisms of bronchial hyperreactivity, these findings represent a small but satisfying step forward. They also have important implications with respect to the regulation of ambient air quality in the United States. Sulfur dioxide is produced by any industry using petrochemicals as a source of power. The principal sources of sulfur dioxide in the US are refineries, foundries and any other industries that generate electrical power by burning oil or coal. America has been described as the Saudi Arabia of coal, and increased use of coal has been advocated as a way of reducing our dependency on imported oil. Our coal is rich in sulfur and is therefore a potential source of large quantities of sulfur dioxide in the next 25 to 50 years.

Clean Air Act

A review of the provisions of the current Clean Air Act will explain why our findings are considered important by both regulatory agencies and industries that generate sulfur dioxide. The original Clean Air Act of 1963 and the Air Quality Act of 1967 both suffered from the same deficiency—they relied on voluntary cooperation by individual states. The states were reluctant to be the first to set stringent standards for fear that they would then be put in a noncompetitive position for attracting industry. The Clean Air Act amendments of 1970 were especially important in that they established the first comprehensive program for attacking air pollution nationwide. Several very important features were included in

these amendments. One feature was to establish the Environmental Protection Agency (EPA), which was required to set national air-quality standards that were to be attained by 1975. States were charged with developing plans for achieving these standards, and the plans were subject to the EPA's approval. These plans differed in states with different problems. In the industrial Northeast, for example, the plans involved modifying existing industrial plants so that the quantity of pollutants emitted would be reduced. In California where photochemical pollution is a greater problem, the plans included setting tougher standards for automobile emissions. The Clean Air Act amendments also specified that the EPA was authorized to set emission limits for new sources of pollutants in any part of the country. As the result of this provision, new power plants generate only 12 lb (5.4 kg) of sulfur dioxide per ton (907 kg) of coal consumed, whereas old plants generate as much as 83 lb (38 kg) per ton of coal—a sevenfold difference. Other standards have resulted in substantial reductions in hydrocarbons, nitrogen oxide and carbon monoxide from automobiles. The EPA was additionally authorized to levy fines on industries that failed to comply with its directives, and the fines were to be sufficiently great to offset whatever economic advantage an industry may have gained by failing to comply to the Clean Air Act. States and even individual citizen groups may bring civil action against polluters, providing further impetus for enforcement.

By developing a comprehensive plan for controlling pollution, and by granting specific, effective enforcement powers, the Clean Air Act amendments of 1970 have resulted in improvement in air quality, especially for the pollutants specified in the Clean Air Act as requiring regulation ("criteria pollutants"). The procedure that is followed in establishing a national standard for a pollutant is as follows: first, the EPA prepares a criteria document summarizing the epidemiologic, toxicologic and clinical studies that are relevant to that agent. Once the criteria document has been reviewed by invited consultants, the EPA administrator then publicizes the document, proposes standards for the pollutant and invites response from the public. After the public has had a chance to respond and the proposals have been reviewed by an independent advisory committee, the final promulgation of standards is made.

The law requires that the primary standards for a pollutant protect sensitive groups of the population against adverse health effects and that the standards ensure a margin of safety between the "probable effects level" and the level permitted. The standard is to be defined on the basis of health alone; consideration of the cost of achieving standards is not permitted. The standards for sulfur dioxide are that the average level of sulfur dioxide over 24 hours not exceed 0.14 ppm on more than one day each year, and that the average annual concentration not exceed 0.03 ppm. There is no short-term standard for sulfur dioxide, and the 24-hour standard of 0.14 ppm means that the level could be very much higher for short periods as long as the level was much lower at other times in the day. If, for example, sulfur dioxide levels were low throughout the night, the average daily level might remain below 0.14 ppm despite quite high levels of SO_2 during working hours. Our finding that people with mild asthma may develop bronchospasm on inhaling sulfur dioxide for five minutes suggests that under the provisions of the current law, a short-term standard is required if sensitive groups are to be protected with a margin of safety.

Spokesmen for industries and independent investigators have disputed the relevance of these findings to what they call "real life" conditions. One of the criticisms of our work, for example, is that our subjects breathed through a mouthpiece during their exposure to sulfur dioxide, bypassing the important defensive functions of the nose.[18] It is argued that our findings may therefore be considered irrelevant to environmental standards for sulfur dioxide. This particular criticism is specious because with viral rhinitis or any of the common causes of nasal obstruction, most ventilation must pass through the mouth. People with asthma often also have allergic rhinitis and therefore have a higher incidence of nasal obstruction. Furthermore, ventilation shifts from being predominately nasal to oronasal with exercise, increasing the proportion of ventilation that bypasses the nose. Kirkpatrick and associates[19] directly investigated the importance of the defensive role of the nose by comparing the response of people with asthma who were exposed to sulfur dioxide while wearing a face mask that permitted breathing through both the nose and the mouth to the response in the same subjects exposed while breathing through the mouth alone. The response was only slightly lessened when his subjects breathed through the face mask, and symptomatic

bronchospasm still occurred on inhaling 0.5 ppm of sulfur dioxide during light exercise.

Another approach to dealing with data such as ours is to change the law. The Business Round Table, a group of industrial representatives, has proposed that the definition of adverse health effects be changed to "a permanent or incapacitating illness." This change in definition would mean that transient, distressing, but not incapacitating, bronchospasm would not be considered relevant to standards for sulfur dioxide. Another proposal is that the requirements to protect sensitive groups be eliminated because a few individuals abnormally sensitive to almost any material can be found in a nation of 250 million people. The Business Round Table further proposes that the concepts of "probable effect levels" and of "a margin of safety" be replaced with the concept of "acceptable risk," and that the definition of what is an acceptable risk be made with consideration of the costs of achieving standards. A problem with this proposal is that it is difficult to determine the costs of achieving a standard because estimates of cost are based on available technology and until the passage of the amendments in 1970, there was virtually no incentive for developing technology to reduce the emission of pollutants economically. Considering costs also requires that some dollar value be ascribed to suffering, and suffering is disproportionately shared. That is, sensitive groups may suffer marked distress while the rest of us notice no effect.

A final approach to dealing with data showing adverse health effects from atmospheric pollution is to change the personnel responsible for enforcing the Clean Air Act. The San Francisco *Examiner* recently reported that of the 15 people appointed to the Environmental Protection Agency by the Reagan administration, 11 have worked for the industries that the EPA regulates, such as the steel, paper and chemical industries. The public has cause to worry that this change in the personnel responsible for enforcing air-quality standards may severely threaten the progress this nation has made in cleaning its air and may prevent any further progress in dealing with other potentially serious problems, such as the acidification of our lakes and waterways by acid rain.

Conclusion

Our work has shown that people with asthma are abnormally sensitive to inhalation of sulfur dioxide and that bronchospasm may develop if they pursue activities that require light exercise while breathing air containing a level of sulfur dioxide permitted by current ambient air-quality standards. The provisions of the Clean Air Act of 1970 require that sensitive groups in the population be protected against adverse health effects, and our data therefore indicate the need for a short-term standard for sulfur dioxide. The cost of attaining such a standard is unknown. In any case, under current law cost is irrelevant to the process of setting standards; consideration of cost is permitted only in designing plans for achieving standards.

The decision as to whether the health of sensitive subgroups in our population should continue to be protected is an important one. This decision should be made only after the issue has been explicitly stated for discussion and debate by the American public.

REFERENCES

1. Firket J: The cause of the symptoms found in the Meuse Valley during the fog of December 1930. Bull Mem Acad R Med Belg 11:683, 1931

2. Schrenk HH, Heimann H, Clayton GD, et al: Air Pollution in Donora, Pennsylvania—Epidemiology of the Unusual Smog Episode of October 1948. Public Health Bulletin 306. Washington, DC, U.S. Government Printing Office, 1949

3. Logan WPD: Mortality in London fog incident. Lancet 1: 336-338, 1953

4. Buechley RW, Riggan WB, Hasselblad V, et al: SO_2 levels and perturbations in mortality—A study in the New York-New Jersey metropolis. Arch Environ Health 27:134-137, Sep 1973

5. Lambert PM, Reid DD: Smoking, air pollution, and bronchitis in Britain. Lancet 1:853-857, 1970

6. Lunn JE, Knowelden J, Handyside AJ: Patterns of respiratory illness in Sheffield infant school children. Br J Prev Soc Med 21:7-16, 1967

7. Goldstein IF, Block G: Asthma and air pollution in two city areas in New York City. J Air Pollut Control Assoc 24: 665-670, 1974

8. Zeidberg LD, Prindle RA, Landau E: The Nashville Air Pollution Study—I. Sulfur dioxide and bronchial asthma—A preliminary report. Am Rev Respir Dis 84:489-503, 1961

9. Frank NR, Amdur MO, Worcester J, et al: Effects of acute controlled exposure to SO_2 on respiratory mechanics in healthy male adults. J Appl Physiol 17:252-258, 1962

10. Sheppard D, Wong WS, Uehara CF, et al: Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. Am Rev Respir Dis 122:873-878, 1980

11. Boushey HA, Holtzman MJ, Sheller JR, et al: State of the art—Bronchial hyperreactivity. Am Rev Respir Dis 121:389-413, 1980

12. DeKock MA, Nadel JA, Zwi S, et al: New method for perfusing bronchial arteries—Histamine bronchoconstriction and apnea. J Appl Physiol 21:185-194, 1966

13. Simonsson BG, Jacobs FM, Nadel JA: Role of autonomic nervous system and the cough reflex in the increased responsiveness of airways in patients with obstructive airway disease. J Clin Invest 46:1812-1818, Nov 1967

14. Holtzman MJ, Sheller JR, DiMeo M, et al: Effect of ganglionic blockade on bronchial reactivity in atopic subjects. Am Rev Respir Dis 122:17-26, 1980

15. Nadel JA, Salem H, Tamplin B, et al: Mechanism of bronchoconstriction during inhalation of sulfur dioxide. J Appl Physiol 20:164-167, 1965

16. Sheppard D, Saisho A, Nadel JA, et al: Exercise increases sulfur dioxide induced bronchoconstriction in asthmatic subjects. Am Rev Respir Dis 123:486, 1981

17. Koenig JQ, Pierson WE, Frank R: Acute effects of inhaled SO_2 plus NaCl droplet aerosol on pulmonary function in asthmatic adolescents. Environ Res 22:145-153, 1980

18. Proctor DF: Oronasal breathing and studies of effects of air pollutants on the lungs. Am Rev Respir Dis 123:242, 1981

19. Kirkpatrick MB, Sheppard D, Nadel JA, et al: Effect of the oronasal breathing route in the bronchoconstrictor response to sulfur dioxide in exercising asthmatic subjects. Clin Res (in press) 1981

Important Advances in Clinical Medicine

Epitomes of Progress—Physical Medicine and Rehabilitation

The Scientific Board of the California Medical Association presents the following inventory of items of progress in physical medicine and rehabilitation. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in physical medicine and rehabilitation which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Physical Medicine and Rehabilitation of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Nonverbal Communication

THERE ARE MANY disabled persons who are unable to verbally communicate despite an intact awareness and mental competence to express their thoughts and understand spoken words. Recent innovations have provided communication devices for postlaryngectomy persons and equipment for deaf people to communicate by telephone and watch television with subtitles. Unfortunately, many disabled persons lacking the ability to verbally communicate have other impairments that preclude their using these devices, such as cerebral palsy or other brain injury, amyotrophic lateral sclerosis and stroke.

Managing the severely handicapped nonverbal person requires a health care team dedicated to the improvement of nonverbal communication. These teams usually consist of a physician with special training in the field, a speech therapist, physical therapist, occupational therapist and psychologist.

Recent articles explain the process that determines which persons would be appropriate candidates for nonverbal communication training and which of the increasing numbers of devices would be most suitable for a particular disability. Items to investigate include: attention span, areas of volitional motor control, aphasia, memory and so forth.

The advent of microswitches and computer chips has aided the development of devices that are much more portable and becoming less expensive. The most obvious form of communication, if the ability to use it exists, is the typewriter. A small portable device about the size of a minicassette recorder (called the Cannon Communicator) enables a person to type out messages on a small tape. Someone with severe cerebral palsy may have difficulty using this device, however, because of limited volitional motor control. Some devices can be controlled by one muscle through an electromyokinetic signal or use of a finger or toe switch.

It is extremely gratifying to help patients communicate. For example, a young man with a head injury was seen, whose only voluntary motor movement was very slight movement of his thumb. He was able to use a communication

board and learned to communicate effectively with his family and hospital staff.

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REFERENCES

Coleman CL, Cooks AM, Meyers LS: Assessing non-oral clients for assistive communication devices. J Speech Hear Disord 45: 515-526, Nov 1980

Shane HC, Bashir AS: Election criteria for the adoption of an augmentative communication system: Preliminary considerations. J Speech Hear Disord 45:408-414, Aug 1980

Phrenic Nerve Conduction Studies

LONG-TERM TOTAL or partial ventilatory support by diaphragm pacing (electrophrenic respiration) is now an accepted procedure in quadriplegic patients with chronic respiratory paralysis or insufficiency and in patients with brain stem lesions, sleep apnea and other respiratory disorders. The primary requirement for successful diaphragm pacing is viability of the phrenic nerves, which should be assessed preoperatively. This is done by phrenic nerve conduction studies.

A method has been available since 1967 for studying phrenic nerve conduction by percutaneous stimulation of that nerve in the neck and placing surface recording electrodes on the chest. However, the technique has not become a routine procedure in most electrodiagnostic laboratories for a number of reasons, including difficulty with simultaneous stimulation of the brachial plexus, problems with recording the evoked potential and patient discomfort.

A recent paper describes a simple, safe, reliable and relatively painless method for studying phrenic nerve conduction. The technique uses a transcutaneous monopolar-needle stimulating electrode and surface recording electrodes, the active pickup being positioned over the xiphoid process and the reference electrode at the ipsilateral costochondral junction of the eighth intercostal space. Normal measurements are (mean ± standard deviation): latency 7.44 ± 0.59 msec, amplitude 845 ± 405 μV, and duration 48.1 ± 12.2 msec. Latency is the most important measurement. That paper reported that single determinations of phrenic nerve conduction had been done in a few quadriplegic patients but concluded that serial determinations are indicated in most patients requiring diaphragm pacing.

Another recent paper reports serial phrenic nerve conduction studies in quadriplegic patients. This study showed a pattern of phrenic nerve function that changed with time. Phrenic nerves may be responsive initially, then become unresponsive and have responses reappear later. In other patients, the phrenic nerves may be unresponsive initially and responsive later in the post-injury course. Finally, some nerves may remain nonviable once responses are lost. The report concluded that when considering diaphragm pacing serial studies should be carried out for at least six weeks after injury on initially responsive nerves and for at least two years after injury on initially unresponsive nerves before a final decision is made regarding phrenic nerve viability.

Phrenic nerve conduction studies have also been useful in differentiating between neurogenic and nonneurogenic causes of hypoventilation in patients with craniocervical trauma and in patients for whom there are problems in discontinuing respirator care. In view of the recent technical advances, phrenic nerve conduction studies should be used by electrodiagnosticians in centers dealing with patients with any of these disorders.

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REFERENCES

Lieberman JS, Corkill G, French BN: Phrenic nerve conduction studies in the evaluation of ventilatory problems in patients with cranio-cervical trauma. Surg Neurol 10:205-208, Sep 1978

Lieberman JS, Corkill G, Nayak NN, et al: Serial phrenic nerve conduction studies in candidates for diaphragm pacing. Arch Phys Med Rehabil 61:528-531, Nov 1980

MacLean IC, Mattioni TA: Phrenic nerve conduction studies: A new technique and its application in quadriplegic patients. Arch Phys Med Rehabil 62:70-73, Feb 1981

Evoked Brain Potentials in Head Trauma

EVOKED POTENTIALS, signals that are buried in spontaneous electrical activity of the brain, can be evaluated using signal-averaging techniques. These noninvasive electrophysiologic tests localize dysfunction in individual neurosystems and identify damaged anatomic areas of the brain. This information complements that obtained by clinical evaluation and computerized tomography in brain trauma. Grading the evoked brain potentials allows assessment of the degree of abnormality and accurately establishes a prognosis for rehabilitation soon after head injury occurs.

Each sensory modality allows exploration of cortical and subcortical areas—the auditory evoked potential assesses the brain stem and the vertex, somatosensory evoked potentials assess deep subcortical structures and the primary somatosensory area and visual evoked potentials assess the occiput. There appears to be a definite relationship between the degree of disruption of

central nervous system function in brain trauma and the degree of abnormality of evoked potential.

In the postconcussion syndrome, evaluation of brain evoked potentials may also establish that though there are no abnormal physical signs, there may in fact be an electrophysiologic disturbance between the diencephalon and the brain stem. This finding implies an organic rather than a psychogenic basis for this syndrome.

The evoked potential technique can distinguish between organic and psychogenic disorders, provide an objective indicator of sensory function when perceptual tests are impractical (such as with comatose persons) and disclose the specific brain activities that handle different types of sensory information. Evoked potentials can provide information on impairment of ipsilateral, contralateral or bilateral transmission of electrical signals and can delineate the most intact sensory systems, thereby aiding in the planning of the most appropriate rehabilitation strategies.

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REFERENCES

Greenberg RP, Mayer DJ, Becker DP, et al: Evaluation of brain function in severe human head trauma with multimodality evoked potentials—Part I. Evoked brain-injury potentials, methods, and analysis. J Neurosurg 47:150-162, Aug 1977

Noseworthy JH, Miller J, Murray TJ, et al: Auditory brainstem responses in postconcussion syndrome. Arch Neurol 38:275-278, May 1981

Rappaport M, Hall K, Hopkins K, et al: Evoked brain potentials and disability in brain-damage patients. Arch Phys Med Rehabil 58:333-338, Aug 1977

Bladder-Sphincter Dyssynergia

MICTURITION IN ADULTS is under voluntary control and is well coordinated when contraction of the bladder is associated with relaxation of the periurethral sphincter. Any spinal cord lesion involving the long tracts results in some loss of voluntary control on micturition and bladder-sphincter incoordination or dyssynergia in which voluntary or reflex contraction of bladder does not lead to complete relaxation of periurethral sphincter. Mild dyssynergic response occurs with multiple sclerosis and incomplete spinal cord injuries. Severe detrusor-sphincter dyssynergia occurs in complete upper thoracic and cervical lesions and is associated with a rise in both systolic and diastolic blood pressures. Lesions above the pons, such as stroke or head injury, are usually associated with detrusor hyperreflexia and not dyssynergia.

Detrusor-sphincter dyssynergia with increased sustained intravesical pressure can lead to vesicoureteral reflux and damage to the kidneys. Mild dyssynergia is treated with alpha blockers such as phenoxybenzamine hydrochloride, anticholinergics and intermittent catheterization. Severe dyssynergia is best treated by a transurethral resection (myotomy) of the sphincter. Spinal cord injury patients with detrusor-sphincter dyssynergia and maintained with long-term indwelling catheters or supravesical divisions run the risk of autonomic dysreflexia, repeated infections and stone disease.

Removal of the catheter in such patients following transurethral sphincterotomy reduces the incidence of repeated infections and autonomic dysreflexia and improves the quality of life.

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REFERENCES

Perkash I: Detrusor-sphincter dyssynergia and dyssynergic responses: Recognition and rationale for early modified transurethral sphincterotomy in complete spinal cord injury lesions. J Urol 120:469-474, Oct 1978

Perkash I: Pressor response during cystomanometry in spinal injury patients complicated with detrusor-sphincter dyssynergia. J Urol 121:778-782, Jun 1979

Perkash I: Problems of decatheterization in long-term spinal cord injury patients. J Urol 124:249-253, Aug 1980

Current Concepts on Orthotics

THE USE OF ORTHOSES (braces and splints) has greatly expanded in recent years due to better understanding of the principles of use, the fabrication of new and lighter materials and increased acceptance by wearers.

The basic principles of supporting weakness, preventing or correcting deformities and relieving pain have not changed since ancient times, but with newer knowledge these principles are being applied more effectively. For example, the use of a cast brace to maintain knee motion, rather than rigidly immobilizing the knee, will give better functional end results. Also, the ankle-foot orthosis (AFO) to correct drop foot has replaced the short-leg metal brace attached to a shoe. It is a simple plastic posterior shell that fits from the calf along the sole of the foot and into the shoe. New plastics have aided the fabrication of leg braces and back supports, from the simple to the more complicated ones, including the Milwaukee frame for scoliosis.

Spinal orthotics, which formerly relied on a three-point pressure system made of leather and metal, have given way to the thoracolumbar spinal orthosis (TLSO) made of plastic that secures support around the pelvis and extends upward to give support in any posture.

Shoe orthoses vary from a special cast to fit a deformed foot or appropriate wedges to relieve pressure to special plastic insoles that accommodate for pressure areas in neuropathy.

The upper extremity orthosis not only substitutes for weak or absent motor power but also maintains position so that adjacent joints can either be moved or given traction by special attachments. Again, the newer plastics have made these orthoses more effective and acceptable to users.

A patient who is temporarily or permanently disabled can be helped by a profusion of devices ranging from a longhandled shoehorn and stocking puller-on to pencil holders and knife-fork devices. There are many kinds of canes, crutches and walkers with varying types of supports for particular problems. Wheelchairs also come in a variety of sizes, shapes and features to accommodate special needs.

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REFERENCES

Mastro BA, Mastro RT: Selected Reading, A Review of Orthotics and Prosthetics. Alexandria, VA, The American Orthotic and Prosthetic Association, 1980

Redford J: Orthotics, Etcetera. Baltimore, Williams and Wilkins, 1980

Electrodiagnostic Evaluation of Carpal Tunnel Syndrome

CARPAL TUNNEL SYNDROME (CTS) is a clinical condition for which electrodiagnostic testing is commonly requested. Routine electrodiagnostic testing for CTS usually includes electromyography (EMG) of the involved extremity and recording the median nerve distal motor latency (DML), distal sensory latency (DSL) to the index finger and forearm conduction velocity. Unfortunately, these routine procedures are limited in their accuracy. EMG gives abnormal results in only 45 percent of cases of CTS, while median nerve DML is abnormal in 67 percent of cases and DSL is abnormal in 85 percent of CTS cases. Thus, at least 15 percent of cases with apparent clinical CTS will have normal electrical studies. Because of this high rate of false-negative findings on electrical studies a number of procedures have recently been proposed to improve electrodiagnostic accuracy in CTS.

As early as 1974 data were reported that showed that abnormal findings on DSL, the most sensitive single test, could be limited to a single digital branch of the median nerve in 10 percent of CTS cases. Recording of the DSL to multiple digits (not yet a routine procedure) is done using the same measured distance from stimulating cathode to pick-up cathode for each digit. This technique may be useful in cases with a high probability of CTS on clinical grounds where there is a normal DSL to the index finger. It is especially indicated when there is disturbed sensation in a finger other than the index finger and the routine studies are normal.

Of great clinical interest are recent data that show a well-defined relationship between median and ulnar DML and DSL in the same and opposite hands. The difference in median nerve DML and DSL between opposite hands should not exceed 1 msec and 0.5 msec, respectively. Likewise, the difference between median and ulnar nerve DMLs and DSLs in the same or opposite hand should not exceed 1 msec and 0.5 msec, respectively. Differences in excess of the above values suggest dysfunction of the nerve with the longer latency if all latencies are within the normal range. Many cases of CTS can be identified by this technique when routine DML and DSL recordings are normal. Because CTS is bilateral in over 60 percent of patients, the use of the median-ulnar nerves latency difference seems the more reliable tool in diagnosis when the routine studies are reported in the normal range.

A recently reported addition to the median-ulnar nerves latency difference technique is comparison of the median and ulnar nerve DSL with the ring finger, which is usually innervated by both nerves. Patients with normal findings showed a difference of 0.5 msec or less, while patients with CTS showed a difference ranging between 1 and 2.1 msec (mean 1.46 msec).

Finally, techniques that evaluate the more discrete segments of the terminal median nerve are reported to be helpful in the diagnosis of CTS and especially in the differentiation between CTS and a distal neuropathy. One study compares conduction between the wrist-palm segment and the palm-digit segment of the nerve. Another study uses multiple stimulation sites at 1-cm increments and looks for a change in uniform latency with increasing distance. While both techniques are complicated, they may be valuable in difficult CTS cases. The study of multiple stimulation sites is especially useful in identifying a discrete site of abnormality in the carpal tunnel.

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REFERENCES

Felsenthal G: Median and ulnar distal motor and sensory latencies in the same normal subject. Arch Phys Med Rehabil 58:297-302, Jul 1977

Felsenthal G, Spindler H: Palmar conduction time of median and ulnar nerves of normal subjects and patients with carpal tunnel syndrome. Am J Phys Med 58:131-138, Jun 1979

Johnson EW, Kukla RD, Wongsam PE, et al: Sensory latencies to the ring finger: Normal values and relation to carpal tunnel syndrome. Arch Phys Med Rehabil 62:206-208, May 1981

Kimura J: The carpal tunnel syndrome: Localization of conduction abnormalities within the distal segment of the median nerve. Brain 102:619-635, Sep 1979

Thrombolytic Therapy for Deep Venous Thrombosis and Pulmonary Embolism

A MAJOR PROBLEM associated with spinal cord injury is deep venous thrombosis (DVT) and its dreaded concomitant, pulmonary embolism (PE). These entities traditionally have been treated with intravenously administered heparin anticoagulation, followed by three to six months of anticoagulation with warfarin sodium taken orally.

Another promising treatment modality, thrombolytic therapy, is now available to clinicians. Anticoagulation therapy using heparin does not prevent recurrent attacks of deep venous thrombosis, improve hemodynamic disturbances associated with thrombosis or embolism, or prevent permanent impairment of the pulmonary vascular bed and venous valves. There is evidence that lysis of thrombi and emboli using streptokinase (SK) or urokinase (UK) followed by heparin anticoagulation can achieve all these goals. Both SK and UK are plasminogen activators; they convert inactive plasminogen to the active enzyme plasmin, which in turn dissolves fresh fibrin clots.

At a recent National Institutes of Health Consensus Development Conference, the following guidelines were set forth for the use of thrombolytic therapy. This therapy should be administered only in cases where benefits outweigh risks, such as in patients with proved, fresh (less than five days) proximal deep venous thrombosis, pulmonary embolism or both. Proper patient selection is mandatory because bleeding, the most critical side effect, occurs when there are hemostatic defects present before instituting therapy. Absolute contraindications include active internal bleeding, cerebrovascular accident within the previous two months or other active intracranial process. Major contraindications include recent surgical procedure (within the past seven to ten days) obstetric delivery, organ biopsy, previous puncture of noncompressible vessels, gastrointestinal bleeding, serious trauma or severe hypertension. Minor contraindications include recent (within the past seven to ten days) minor trauma, high likelihood of left heart thrombus, bacterial endocarditis, hemostatic defects and patient's age being over 75 years.

Thrombolytic drugs are administered in a fixed loading dose, followed by a fixed maintenance dose for 24 hours. This is in turn followed by conventional therapy with heparin for seven to ten days, followed by warfarin (Coumadin, Panwarfin).

Bleeding can be minimized by limiting physical handling of the patient, discontinuing intramuscular and subcutaneous injections and substituting medications taken by mouth, minimizing needle punctures and compressing invaded vessels. When this regimen is followed, the incidence of major bleeding complications has been 5 percent.

Therapy is monitored by following activated partial thromboplastin time and prothrombin time to determine whether some degree of systemic fibrinolysis has been established. Monitoring is not used as a guide for altering drug dose.

If bleeding should occur, therapy is discontinued. This usually results in cessation of fibrinolysis, as these therapeutic agents have a short half-life. If bleeding continues, whole fresh blood, fresh frozen plasma or epsilon aminocaproic acid (Amicar) can be administered.

Fibrinolytic therapy is a promising development in the treatment of DVT and PE and may eventually become the initial form of therapy for these conditions.

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REFERENCES

NIH Consensus Development Conference summary. South Med J 73:1525-1526, Nov 1980

Sasahara A, Ho D, Sharma GVRK: When and how to use thrombolytic agents. Drug Therapy (Hosp), Oct 1979, pp 20-32

Sharma GVRK, Burleson VA, Sasahara AA: Effect of thrombolytic therapy on pulmonary-capillary blood volume in patients with pulmonary embolism. N Engl J Med 303:842-845, Oct 9, 1980

Diagnosing Pulmonary Embolism

DESPITE THE WIDESPREAD USE of low-dose heparin therapy as prophylaxis against deep vein thrombosis (DVT), that complication and its sequela, pulmonary embolism (PE), are relatively common in patients with spinal cord injury, head injury, stroke or major fractures. Patients at high risk for complications from anticoagulant therapy are those with (1) cerebral hemorrhage, (2) completed strokes within two months of onset, (3) recent head injury, (4) spinal cord injury with associated intracranial, intrathoracic or intra-abdominal injuries, (5) peptic ulcer disease or a bleeding diathesis or (6) prior compli-

cations with anticoagulant drugs. A brief update on the diagnosis of pulmonary embolism is therefore included in this series of epitomes on physical medicine and rehabilitation.

Current practice in suspected PE may include initiation of anticoagulation on clinical criteria alone. However, physical signs and symptoms typically are nonspecific. More commonly, treatment is begun after arterial blood gas studies and ventilation-perfusion ($\dot{V}/\dot{Q}$) lung scanning. However, these approaches may result in misdiagnosis and inappropriate and hazardous treatment in many cases. A low arterial oxygen pressure (Po_2) may be present with a variety of acute or chronic lung diseases while a normal Po_2 may occur in up to 15 percent of patients with documented PE. $\dot{V}/\dot{Q}$ scanning has been regarded as an adequate screening test for PE in terms of sensitivity and specificity, although a recent report questions the validity of this concept. False-positive findings on $\dot{V}/\dot{Q}$ scans are common, occurring in from 60 percent to 80 percent of cases when pulmonary angiography is used to confirm the presence of PE. False-negative findings of PE on $\dot{V}/\dot{Q}$ scans, however, are rare. Thus, normal findings on $\dot{V}/\dot{Q}$ scan virtually rule out the presence of PE if done between 24 and 72 hours from onset of symptoms.

The diagnosis of PE usually leads to such treatment as administration of anticoagulant drugs or vena cava ligation, both of which may have serious complications. Thus, pulmonary angiography to assure that PE is present is recommended in situations where PE is suspected and the $\dot{V}/\dot{Q}$ scan is positive for PE. These situations include cases in which patients have parenchymal lung disease or abnormalities in both ventilation and perfusion scans (because of the very high rate of false-positive scans), and cases in which patients are being considered for vena cava ligation or in whom anticoagulant drugs are contraindicated or who are at high risk for complications from anticoagulation therapy.

The importance of pulmonary angiography to confirm the presence of PE in patients at high risk for complications from anticoagulation therapy is just beginning to be realized. Carrying out potentially dangerous therapy in a patient who does not require it is hazardous. Heparin is the leading cause of adverse drug reactions in patients in hospital and anticoagulant drugs taken orally pose similar problems. Although pulmonary angiography is not a screening procedure, it is the procedure of choice for confirming the diagnosis of PE in high-risk patients.

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REFERENCES

Giudice JC, Komansky HJ, Gordon R: Pulmonary thromboembolism—I. Current concepts in pathogenesis and diagnosis. Postgrad Med 67:64-71, 74-75, 77, May 1980

Robin ED: Overdiagnosis and overtreatment of pulmonary embolism: The emperor may have no clothes. Ann Intern Med 87:775-781, Dec 1977

Viamonte M Jr, Koolpe H, Janowitz W, et al: Pulmonary thromboembolism—Update. JAMA 243:2229-2234, Jun 6, 1980

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EDITORIALS

Of Minorities, Majorities, Medicine and Health

WHAT HAS HAPPENED to majority rule? It is still an article of faith that our government expresses the will of the majority and that indeed decisions are made by a vote of the majority wherever the democratic process is operative. But in practice is it a real majority that always makes the decisions? Often it seems that what is decided is actually the product of interaction and negotiation among the parties with most at stake which are nearly always numerical minorities with one or another kind of special interest. It is relatively seldom that one senses that the real majority has spoken and been heard. The passage of Proposition 13 in California (which has had national repercussions) might be cited as one of the rare examples in recent years where the majority spoke as the majority on an issue, and was heard. More often the will of the real majority is unfocused and the democratic process in government rather seems to reflect the will of well-organized (and often well-funded) special interest groups rather than the views of an ordinarily less aggressive and less focused majority.

Perhaps it was ever thus, and perhaps it can never be otherwise. In any case our social, economic and political system is becoming more complex and interdependent and also is comprised of an increasing number of more or less autonomous and independent groups and entities. It is only natural that these should band together in various combinations to promote their own common interests within the interdependent whole. And it is only natural that they marshal the resources and develop the skills to advocate their causes and interests as effectively as possible within this whole. And every year this process becomes more refined and special interest advocates are becoming more powerful and indeed more successful.

The medical profession finds itself in the thick of these developments, and as a social, economic and political minority has performed with commendable skill and effectiveness in this very real world. But unlike most of the other minority special interest groups, the medical profession—because of its professional expertise—plays a larger role as advocate for the health and health care of all the individual persons who are or may become patients (actually the social, economic and political majority). In yet another dimension it acts as the advocate for the health and well-being of the environment in which everyone, both the numerical majority and all the numerical minorities, must live. In these dimensions the special interest of the medical profession as a social, economic and political minority is much larger than just the protection and advancement of its self-interests as a profession. The medical profession can and should be the advocate and spokesman for the undifferentiated majority in virtually anything pertaining to health and health care.

During the past few decades the medical profession in America has become much more active and aggressive in matters social, economic and political. Its advocacy may be expected to become even more effective if it can become identified as the recognized authoritative advocate of the interests not only of minorities, but also of the majority

in matters of health and health care. And one may safely predict that as the anticipated glut of physicians becomes a reality, many more physicians will have time and energy to give to the social, economic and political advocacy of the profession in these wider dimensions of professional responsibility. If and as this occurs, and if and as the profession itself develops the necessary leadership, public support will develop to a much greater extent than has been the case so far. And if and when this happens, the social, economic and political majority will come to have a voice and an advocate in the medical profession to express the real majority's real interests in health and health care.

—MSMW

Management of Bleeding Esophageal Varices

THE HOPE THAT randomized trials would make the treatment of variceal bleeding rational has not been realized, nor is it likely to be. In both cooperative trials and single-hospital studies there seems no escape from problems of (1) preselection of patients by patterns of referral, (2) diminishing populations being treated in specialized centers because of skilled surgery practiced in community hospitals, (3) inevitable violations of experimental protocol due to exigencies of care and (4) inability to control for behavior of patients after they leave the hospital.[1,2] Moreover, bias and error affect factors by which the success of treatment should be judged, such as survival rates, assessments of encephalopathy and hepatic function, and the role of the magnitude and direction of portal venous flow in determining outcome.[1,3,4]

No factor dominates results more than the state of the liver. With any reasonable therapeutic program, survival rates in patients with excellent hepatic function will be nearly 100 percent, with mediocre function 50 percent to 60 percent, and with poor function 10 percent to 30 percent.[5,6] The objective is to avoid errors in judgment and technique that worsen these odds.

Rikkers' comprehensive Medical Progress article "Operations for Management of Esophagogastric Variceal Hemorrhage" in this issue provides a discriminating guide to both the facts and equivocations that support these views and the arguments that oppose them. A program useful for managing treatment of bleeding esophageal varices follows.

In a patient with presumed bleeding of varices that does not stop spontaneously, an intravenous drip of vasopressin is prepared to run at 0.3 to 0.4 U vasopressin per minute (4 to 6 μU per kg of body weight per minute, 10 ampules of 200 U vasopressin per 500 ml of 5 percent dextrose solution). Although formerly advised, a discrete intravenous injection of 10 U vasopressin has no proved value and may depress cardiac output without controlling bleeding. Somatostatin and propranolol hydrochloride may be superior to vasopressin, but there is not enough evidence to define their roles in controlling variceal hemorrhage.

If bleeding is refractory to vasopressin, the Minnesota (four-lumen) modification of the Sengstaken-Blakemore tube is introduced, with the gastric balloon inflated with 400 ml of air and the esophageal balloon to 30 to 40 mm of mercury; both the esophageal and gastric ports should be connected to suction after the tube is correctly situated.[7] Traction on the tube is usually neither required nor desirable. Only if bleeding persists is 1-kg traction used to help tamponade a bleeding varix in the upper stomach. Traction must be discontinued within 24 hours to prevent necrosis of the esophagogastric junction.

After stability is achieved, fiberoptic esophagogastroscopy is done to establish the source of bleeding. Gastritis rather than varices will be the culprit a third of the time.[8]

Emergency angiography is not required if the diagnosis is secure and if bleeding is controlled. If bleeding persists, angiography is carried out to investigate the possibilities of hemorrhagic gastritis (which may sometimes be controlled by intraarterial infusion of vasopressin) and of bleeding peptic ulcer (which may be amenable to arterial embolization with polyvinyl alcohol or Gianturco-Wallace coils).[9]

Angiography also delineates portal venous anatomy in preparation for an emergency portacaval shunt when other means fail to control bleeding varices or the portal hypertension-gastritis syndrome. Even though the best-risk patients regularly survive an emergency portacaval shunt, emergency shunts are avoided because they double the overall postoperative mortality of

elective portacaval shunts (for example, 20 percent to 50 percent). Nonetheless, the prompt fall in portal venous pressure after a portacaval shunt almost invariably arrests bleeding from portal hypertension; splenorenal and mesocaval shunts are not so reliable for emergency control. Esophagogastric devascularization or esophageal transection and reanastomosis with the EEA stapler are usually reserved for patients who have had unsuccessful shunts in the past. Except in certain centers[10] percutaneous transhepatic embolization of varices is not done because control is no better than with intravenous vasopressin; any effect is likely to be evanescent.[6,11]

Because recent results of emergency injection sclerotherapy of varices have been over 67 percent successful in controlling acute bleeding,[12-14] emergency shunts should be considered only as a last resort. Repeated sclerotherapy with ethanolamine oleate is the exclusive long-term treatment for poor-risk patients (rating 4 or 5 points on our scale[15]) who would almost certainly die if operated on. With more experience the priority for sclerotherapy in the emergency treatment of bleeding varices may need to be advanced, and repeated sclerotherapy could even be the preferred treatment for all patients with esophageal varices that have bled, though it may not necessarily increase their length of survival.[14]

At the moment, however, I prefer an elective portal-systemic venous shunt. The selective distal splenorenal shunt is the first choice, provided that the splenic vein is over 1 cm in diameter and is oriented so that it can be anastomosed to the left renal vein with good lines of hydrodynamic flow.[16] This shunt is chosen because it is ordinarily an easier operation than a proximal splenorenal shunt with splenectomy and because it probably delays the onset of postoperative encephalopathy in many patients. One should not expect metabolic miracles, inasmuch as the superlative results reported[17] are in part attributable to exclusion of the worst-risk patients (those with ascites or in whom portal venous blood fails to perfuse the liver) and less sanguine reports of mortality and prevalence of encephalopathy will no doubt follow when patients representing the full range of risks are encompassed.[18-21] Assertions that the selective distal splenorenal shunt does not decrease the rate of portal-vein blood flow to the contrary, in one study flow decreased 34 percent ($P<0.001$),[22] and most observers agree that with time its hemodynamics become like those of the side-to-side portacaval shunt.[4]

When the selective distal splenorenal shunt is impractical, there is little to pick between results of the proximal splenorenal shunt with splenectomy and the portacaval shunt,[15] except for the advantage of the proximal splenorenal shunt when the spleen needs to be removed for hypersplenism.[23] The portacaval shunt is usually easier to carry out and clearly conserves vast amounts of blood that would have been lost during repeated variceal hemorrhages, though increased longevity as compared with outcome of patients not operated on is doubtful.[24] The mesocaval shunt does not have any particular advantages, except when anatomic problems such as a blocked portal vein but open superior mesenteric vein dictate its use. No doubt results of all shunt procedures will improve if patients can be convinced to forswear alcohol after surgery.[2,25]

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REFERENCES

1. Malt RA: Portasystemic venous shunts. N Engl J Med 295: 24-29, 80-86, 1976

2. Gordon RS Jr: What should we tell cirrhotics about drinking? Gastroenterology 80:1595-1596, 1981

3. Graham DY, Smith JL: The course of patients after variceal hemorrhage. Gastroenterology 80:800-809, 1981

4. Malt RA, Nabseth DC, Orloff MJ, et al: Portal hypertension, 1979. N Engl J Med 301:617-618, 1979

5. Ottinger LW, Moncure AC: Transthoracic ligation of bleeding esophageal varices in patients with intrahepatic portal obstruction. Ann Surg 179:35-38, 1974

6. Malt RA: Transhepatic embolization of varices: A surgeon's view. J Cardiovasc Intervent Radiol 3:303-304, 1980

7. Malt RA: Control of massive upper gastrointestinal hemorrhage. N Engl J Med 286:1043-1046, 1972

8. Novis BH, Duys P, Barbezat GO, et al: Fibreoptic endoscopy and the use of the Sengstaken tube in acute gastrointestinal haemorrhage in patients with portal hypertension and varices. Gut 17:258-263, Apr 1976

9. Athanasoulis CA: Therapeutic applications of angiography. N Engl J Med 302:1117-1125, 1174-1179, 1980

10. Widrich WC, Robbins AH, Nabseth DC: Transhepatic embolization of varices. J Cardiovasc Intervent Radiol 3:298-303, 1980

11. Smith-Laing G, Scott J, Long RG, et al: Role of percutaneous transhepatic obliteration of varices in the management of hemorrhage from gastroesophageal varices. Gastroenterology 80: 1031-1036, 1981

12. Terblanche J, Yakoob HI, Bornman PC, et al: Acute bleed varices: A five-year prospective evaluation of tamponade and sclerotherapy. Ann Surg 194:521-530, 1981

13. Johnston GW, Rodgers HW: A review of 15 years' experience in the use of sclerotherapy in the control of acute haemorrhage from oesophageal varices. Br J Surg 60:797-799, Oct 1973

14. Tedesco FJ: Endoscopic injection sclerosis (EIS) of esophageal varices: Rebirth of an old technique. Gastrointest Endosc 27:107, 1981

15. Malt RA, Szczerban J, Malt RB: Risks in therapeutic portacaval and splenorenal shunts. Ann Surg 184:279-288, 1976

16. Warren WD: Loss of hepatic portal perfusion after selective shunts. Am J Surg 141:581, 1981

17. Rikkers LF, Rudman D, Galambos JT, et al: A randomized, controlled trial of the distal splenorenal shunt. Ann Surg 188: 271-282, Sep 1978

18. Nabseth DC: The distal splenorenal shunt: An enigma. Am J Surg 141:579-580, 1981

19. Kallio H, Lempinen M: Distal splenorenal shunt for portal hypertension. Ann Chir Gynaecol (Fenn) 70:1-4, 1981

20. Conn HO, Resnick RH, Grace ND, et al: Distal splenorenal shunt vs portal-systemic shunt: Current status of a controlled trial. Hepatology 1:151-160, 1981

21. Fischer JE, Bauer RH, Atamian S, et al: Comparison of distal and proximal splenorenal shunts: A randomized prospective trial. Ann Surg 194:531-544, 1981

22. Maillard JN, Flamant YM, Hay JM, et al: Selectivity of the distal splenorenal shunt. Surgery 86:663-671, Nov 1979

23. Mutchnick MG, Lerner E, Conn HO: Effect of portacaval anastomosis on hypersplenism. Am J Dig Dis 25:929-938, 1980

24. Reynolds TB, Donovan AJ, Mikkelsen WP, et al: Results of a 12-year randomized trial of portacaval shunt in patients with alcoholic liver disease and bleeding varices. Gastroenterology 80:1005-1011, 1981

25. Borowsky SA, Strome S, Lott E: Continued heavy drinking and survival in alcoholic cirrhotics. Gastroenterology 80:1405-1409, 1981

Cheating in Medical School

AT A RECENT MEETING of the Association of American Medical Colleges there was a depressing report on the existence, nay, the prevalence of cheating in medical schools. A study in two unnamed medical schools (which understandably assured anonymity for the schools and the students) reported that some 58 percent of the medical students admitted to having cheated in medical school and that 88 percent of those admitted to having cheated as undergraduates as well. However, the good news is that only 2 percent of the 58 percent who had cheated were frequent cheaters. The extent to which cheating may or may not be a problem in other than the two unnamed schools is not known.

In today's world of medical science and patient care the personal integrity of a research scientist or a practicing physician is a basic given, upon which the whole structure of the advancement of medical knowledge, its transmission to medical students and others, and its use in the day-to-day care of patients rests. This personal and professional integrity is the sine qua non of patients' confidence in their physicians and the public's trust in the medical profession.

It is likely that some of the relatively small number of frequent cheaters may be incorrigible. In the professional and public interest these should be exposed and expelled from the school or from the profession, even at the expense of the time-consuming and costly legal actions that are almost certain to ensue. But it would seem that for most of the involved students, who usually are highly motivated but who may have cheated occasionally, a maturing process of education and counseling may be all that is necessary to correct the problem. This could and should be an essential faculty responsibility for the training of physicians. After all, there is very little need to cheat in medical school, and, after all, it is in medical school that students begin to learn what is expected of every member of this learned and trusted profession.

—MSMW

Uncertainties in Distinction of Typical Primary Hyperparathyroidism From Familial Hypocalciuric Hypercalcemia

Our consultants regard the following as worthwhile: blood sugar, to detect diabetes (usually done on an empty stomach); calcium, to detect hyperparathyroidism; cholesterol, to judge the risk of heart disease . . .

—CONSUMERS UNION[1]

WIDESPREAD MEASUREMENT of multiple analytes in small volumes of serum has accurately and inexpensively led to a rise in the ascertainment rate for hypercalcemia. Studies in the US[2] and England[3] provide estimates that annual testing would uncover 25 new cases of hypercalcemia a year per 100,000 population. If this case-ascertainment rate were stable over a 40-year period, 1 percent of the population would have a diagnosis of hypercalcemia. In an unknown fraction of these hypercalcemic persons the cause is familial benign hypercalcemia or familial hypocalciuric hypercalcemia (FHH).[4,5]

FHH is characterized by autosomal dominant transmission with high penetrance for hypercalcemia at all ages. Hypercalcemia is often asymptomatic, hypercalciuria is rare and standard subtotal parathyroidectomy is usually ineffective in correcting the hypercalcemia. Usual complications of chronic hypercalcemia and hypercalciuria, such as nephrolithiasis, impairment of urine-concentrating ability,[6] and reduced glomerular filtration rate, are uncommon. FHH is associated with abnormal function of the kidneys (high tubular resorption of filtered calcium[7]) and of the parathyroids (mild hyperplasia[8] despite high concentrations of ionized calcium in blood). Cellular insensitivity to extracellular ionized calcium in these two affected organs and perhaps in other organs as well[9,10] might account for this disorder. Cellular insensitivity to extracellular ionized cal-

cium would not protect against complications from supersaturation of extracellular fluids with calcium salts. This supersaturation may account for the occurrence of chondrocalcinosis or pancreatitis in FHH.[10,11,12]

Differentiation of FHH from typical primary hyperparathyroidism is difficult, but the difference in clinical course, including the differing response to subtotal parathyroidectomy, makes this distinction important. Three major features point to the diagnosis of FHH instead of typical primary hyperparathyroidism: recognition of hypercalcemia at an early age (onset of hypercalcemia before age 10 is almost universal in FHH but rare in typical primary hyperparathyroidism[4,5]), hypocalciuric hypercalcemia, and persistent hypercalcemia after standard subtotal parathyroidectomy. Additional features of FHH that are less useful in differential diagnosis include a higher concentration of magnesium in serum[7] and lesser elevations of circulating parathyroid hormone.[13]

Family evaluation is essential for diagnosis of FHH, and diagnostic certainty is directly proportional to the number of affected members in a kindred. FHH has been characterized from studies of several large kindred groups, each containing ten or more members with hypercalcemia,[4,5] but no endocrine features of the multiple endocrine neoplasia syndromes outside the parathyroids. These studies have provided sufficient information to allow secure diagnosis in smaller kindreds. In a recent study of 67 patients referred for evaluation after unsuccessful parathyroidectomy for hypercalcemia, six were found to be index cases of kindreds judged to have FHH, and each of the six kindreds had fewer than ten hypercalcemic members.[14] In this issue, Baxi and VanderLaan in their case report "Familial Hypocalciuric Hypercalcemia" describe a kindred with three members proved to be hypercalcemic, two with persistent hypercalcemia after subtotal parathyroidectomy. Their studies make the diagnosis of FHH likely in this kindred.

In patients with hypercalcemia and the possibility of FHH, indices of urinary excretion of calcium should be analyzed. One helpful index is the ratio of urinary calcium clearance to creatinine clearance.[7,10,14] Even with careful attention to details of urine collection, there is approximately 15 percent overlap for values of this ratio between patients with FHH and typical primary hyperparathyroidism.[10] Since typical primary hyperparathyroidism is more common than FHH, many patients with hypocalciuric hypercalcemia will, in fact, represent typical primary hyperparathyroidism.

A calcium to creatinine clearance ratio below 0.010 should alert a physician to defer parathyroidectomy and initiate family testing for hypercalcemia. Discovery of hypercalcemic relatives may warrant further testing to differentiate FHH from familial multiple endocrine neoplasia type I (with endocrine hyperfunction of parathyroids, pancreatic islets and anterior pituitary) or from familial typical primary hyperparathyroidism.[10] When family testing for hypercalcemia is impossible or inconclusive in a patient with hypocalciuric hypercalcemia, the decision whether or not to proceed with a parathyroid surgical procedure will be particularly difficult. Parathyroidectomy may safely be delayed or omitted for some patients with typical primary hyperparathyroidism. Awareness of FHH should result in a decrease of unnecessary or unsuccessful parathyroid surgical procedures in FHH.

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REFERENCES

1. Anonymous: Those costly annual physicals. Consumer Reports 45:601-606, Oct 1980

2. Heath H III, Hodgson SF, Kennedy MA: Primary hyperparathyroidism: Incidence, morbidity, and potential economic impact in a community. N Engl J Med 302:189-193, Jan 1980

3. Mundy GR, Cove DH, Fisken R: Primary hyperparathyroidism: Changes in the pattern of clinical presentation. Lancet 1: 1317-1320, Jun 1980

4. Foley TP Jr, Harrison HC, Arnaud CD, et al: Familial benign hypercalcemia. J Pediatr 81:1060-1067, Dec 1972

5. Marx SJ, Spiegel AM, Brown EM, et al: Family studies in patients with primary parathyroid hyperplasia. Am J Med 62: 698-706, May 1977

6. Marx SJ, Attie MF, Stock JL, et al: Maximal urine-concentrating ability: Familial hypocalciuric hypercalcemia versus typical primary hyperparathyroidism. J Clin Endocrinol Metab 52:736-740, Apr 1981

7. Marx SJ, Spiegel AM, Brown EM, et al: Divalent cation metabolism—Familial hypocalciuric hypercalcemia versus typical primary hyperparathyroidism. Am J Med 65:235-242, Aug 1978

8. Thorgeirsson U, Costa J, Marx SJ: The parathyroid glands in familial hypocalciuric hypercalcemia. Hum Pathol 12:229-237, Mar 1981

9. Marx SJ, Spiegel AM, Brown EM, et al: Familial hypocalciuric hypercalcemia, *In* DeLuca HF, Anast CS (Eds): Pediatric Diseases Related to Calcium. New York, Elsevier North Holland, 1980, pp 413-431

10. Marx SJ, Attie MF, Levine MA, et al: The hypocalciuric or benign variant of familial hypercalcemia: Clinical and biochemical features in fifteen kindreds. Medicine (Baltimore) 60: 397-412, Nov 1981

11. Spiegel AM, Harrison HE, Marx SJ, et al: Neonatal primary hyperparathyroidism with autosomal dominant inheritance. J Pediatr 90:269-272, Feb 1977

12. Davies M, Klimiuk PS, Adams PH, et al: Familial hypocalciuric hypercalcemia and acute pancreatitis. Br Med J 282: 1029-1031, Mar 1981

13. Marx SJ, Spiegel AM, Brown EM, et al: Circulating parathyroid hormone activity: Familial hypocalciuric hypercalcemia versus typical primary hyperparathyroidism. J Clin Endocrinol Metab 47:1190-1197, Jun 1978

14. Marx SJ, Stock JL, Attie MF, et al: Familial hypocalciuric hypercalcemia: Recognition among patients referred after unsuccessful parathyroid exploration. Ann Intern Med 92:351-356, Mar 1980

CASE REPORTS

Refer to: Spencer CD, Crawford GE: Nontoxic staphylococcal pneumonia with empyema in a renal transplant recipient. West J Med 136:147-149, Feb 1982

Nontoxic Staphylococcal Pneumonia With Empyema in a Renal Transplant Recipient

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IMMUNOSUPPRESSED PATIENTS may be afflicted by unusual, opportunistic pathogens that mimic common illnesses in the symptoms they produce. Conversely, more common infections may present in an atypical fashion, obscuring the classic features that suggest to a clinician a particular, tentative cause and initial choice of therapy. The diagnostic maze thus created may require invasive techniques to successfully reach the goal of the most efficacious therapy with the fewest costly delays en route.[1] We report the case of a woman with a renal transplant who twice had an atypical nontoxic episode of staphylococcal pneumonia. Each time a transtracheal aspiration procedure done on admission to hospital gave a culture-proved diagnosis within 36 hours and led to appropriate therapy.

Report of a Case

A 39-year-old woman had undergone a two-antigen-match transplant in 1976 for treatment of renal failure due to juvenile-onset diabetes mellitus. In recent years her medications have included azathioprine, prednisone, lente insulin, multivitamins, iron, furosemide, propranolol, acetaminophen, diazepam and an oxycodone-acetaminophen combination drug.

In March 1978 she presented with two months of anorexia accompanied by an 11-kg (24-lb) weight loss and two weeks of nonproductive paroxysmal cough, occasionally associated with vomiting. She did not have chills, fever, sweats, shortness of breath or pleuritic chest pain. Her immunosuppressive regimen consisted of prednisone 30 mg every other day and azathioprine 100 mg daily.

Physical examination on admission to hospital disclosed an oral temperature of 38.1°C (100.6°F), the highest she had during her hospital stay. She appeared chronically ill and weak but not toxic. Her respiratory rate was 12, blood pressure 102/56 mm of mercury and pulse rate 92 beats per minute. Examination of the chest elicited no abnormal findings.

Roentgenogram of the chest showed only a lingular infiltrate. Arterial blood studies showed Pao_2 65 mm of mercury, $Paco_2$ 35 mm of mercury and pH 7.50. The leukocyte count was 4,500 per cu mm with 87 percent neutrophils and no band forms. The hemoglobin was 9.1 grams per dl, serum creatinine 0.6 mg per dl and blood glucose 145 mg per dl.

Because of her compromised immune-response state, transtracheal aspiration procedure was done on the day of admission. Gram stain of aspirated specimen revealed Gram-positive cocci in clusters, some within neutrophils. Culture of the transtracheal aspirate specimen and one of three cultures of blood produced *Staphylococcus aureus*. She was treated with 6 grams per day of methicillin sodium for 14 days. On this regimen her symptoms resolved and by the time of discharge she had regained 5 kg (11 lb).

Sixteen months later, at the end of May 1979, she presented with a three-day complaint of intermittent sharp shooting pains under her right breast. Roentgenogram of the chest showed normal findings. Three days later she returned complaining of increasing pleuritic pain with radiation to her back and down her right arm. She had no constitutional symptoms other than her pleurisy. Her immunosuppressive regimen was unchanged.

Physical examination showed a nontoxic, cush-

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Figure 1.—Roentgenogram of chest during second episode showing lingular and right middle lobe infiltration and right-sided empyema.

ingoid-appearing woman in mild distress from her pain. Temperature was 37.8°C (100°F), respiratory rate was 16, blood pressure was 168/90 mm of mercury and pulse was 100. Physical examination showed no change from previous examinations, with the exception of auscultatory findings of bilateral rales heard anteriorly and in the right axillary region.

X-ray studies on admission disclosed a definite lingular infiltrate and a possible infiltrate in the right lobe as well. Arterial blood gas studies showed Pao_2 63 mm of mercury, $Paco_2$ 33 mm of mercury and pH 7.46. The leukocyte count was 12,800 per cu mm with 65 percent neutrophils and 23 percent band forms. Hemoglobin was 12.4 grams per dl, blood glucose 394 mg per dl and serum creatinine 0.8 mg per dl.

Transtracheal aspiration was done, but because of the disappointing amount of material returned, the procedure had to be repeated. Gram stain of the sparse specimen showed rare inflammatory cells and no organisms.

On the morning following admission, the roentgenogram of her chest was reviewed. This showed fluid in the major fissure and a convexity near the costophrenic angle against the right lateral chest wall suggestive of effusion (Figure 1). Serous yellow fluid obtained by thoracentesis had exudative characteristics with a pH of 7.25. The cell count was 9,720 per cu mm (93 percent neutrophils and 7 percent lymphocytes). Gram stain was unrevealing. The following morning, 36 hours after admission, culture of the transtracheal aspirate had grown Gram-positive cocci in clusters; hours later the pleural fluid culture was reported to show growth of the same organism, later identified as *S aureus*. Oxacillin sodium, 8 grams per day given intravenously, was begun. A chest tube was inserted. All isolates of *S aureus* were nontypable on phage testing and showed an identical antibiotic-sensitivity pattern, including sensitivity to penicillin. (The bacteriophage type in the previous episode was 83A/85).

Oxacillin was discontinued and aqueous crystalline penicillin G 12 million units daily was administered intravenously for 14 days, followed by 7 days of penicillin given orally. The chest tube was removed after ten days of drainage. The patient was afebrile for the remainder of her hospital stay. Blood cultures, as well as mycobacterial and fungal cultures of pleural fluid, did not grow pathogens. Acute and convalescent titers showed no evidence of recent infection with influenza A or B, adenovirus, Parainfluenza viruses 1, 2 or 3, mycoplasma, coronavirus or meningococcus. Culture of throat washings for virus produced no growth. Her pleuritic pain resolved with therapy and she was discharged after 23 days in hospital. When seen in follow up she was still free of symptoms and roentgenogram of her chest showed clearing of infiltrates.

Discussion

Early reports of staphylococcal pneumonia emphasized its association with influenza and its toxic fulminating course. In the 1950's an association with underlying debilitating disease was noted[2] and in 1970 a subacute nontoxic form of this pneumonia was described.[3] This first report described two patients whose benign course was attributed to community-acquired strains of staphylococci of low virulence in the absence of a predisposition to viral disease or underlying debility. A second report by Gallis[4] in 1975 described a renal transplant recipient who suffered a subacute form of this disease over a month's time before ultimately coming to open-lung biopsy procedure. However, the patient's course was modified by a two-week course of antibiotics to which the organism was sensitive. Daily steroid therapy may also alter the presen-

tation of empyema. Sahn and co-workers[5] reported three cases of patients with "silent" empyema on daily prednisone equivalent doses of 15, 50 and 80 mg respectively. The patient on 15 mg daily also received tetracycline.

The case described in this report differs in that neither of the two episodes was influenced by the administration of daily steroids or antibiotics prior to admission, though the patient was receiving alternate-day steroid therapy and was using antipyretic analgesic medication. Furthermore, the disease recurred after a 16-month interval and in its recurrence the pneumonia was associated with a pleural empyema.

In this case the first episode was rapidly diagnosed because the Gram stain of transtracheal aspirate suggested a bacterial cause, thus leading to prompt initiation of appropriate therapy.

In the second episode only a single symptom (pleuritic pain) was present in a patient not otherwise appearing ill. The differential diagnoses included pulmonary embolism or bacterial, fungal, viral or parasitic pneumonias. Roentgenographic features suggestive of staphylococcal pneumonia were not present, and Gram stain did not provide a clue to the cause of the illness. Transtracheal aspiration was done immediately, however, leading to a specific diagnosis in 36 hours, which was confirmed on culture of thoracic fluid. This early diagnosis obviated the need for further invasive studies. These two episodes show the potential value of transtracheal aspiration in the diagnostic approach to patients whose immune response has been compromised. This relatively simple technique, performed on admission in each instance, led to prompt diagnosis and altered subsequent management. Other invasive procedures such as bronchoscopy or open-lung biopsy procedure, often needed in such patients, were thus rendered unnecessary.

Summary

This case shows that staphylococcal pneumonia with or without empyema may have a unique, nontoxic presentation in a patient whose immune response is compromised. Transtracheal aspiration procedure may have an important role as part of the aggressive diagnostic approach to immunosuppressed patients.[6]

REFERENCES

1. Williams DM, Krick JA, Remington JS: Pulmonary infection in the compromised host, part I. Am Rev Resp Dis 1976; 14:359-394

2. Fisher AM, Trever TW, Curtin JA, et al: Staphylococcal pneumonia—A review of 21 cases in adults. N Engl J Med 1958; 258:919-928

3. Kuperman AS, Fernandez RB: Subacute staphylococcal pneumonia. Am Rev Resp Dis 1970 Jan; 101:95-100

4. Gallis HA: Subacute staphylococcal pneumonia in a renal transplant recipient. Am Rev Resp Dis 1975 Jul; 112:109-112

5. Sahn SA, Lakshminarayan S, Char D: "Silent" empyema in patients receiving corticosteroids. Am Rev Resp Dis 1973 May; 107:873-876

6. Ramsey PG, Ruben RH, Tulkoff-Rubin NE, et al: The renal transplant patient with fever and pulmonary infiltrates: Etiology, clinical manifestations and management. Medicine 1980; 59:206-222

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Familial Hypocalciuric Hypercalcemia

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FAMILIAL BENIGN HYPERCALCEMIA was first described by Foley and his group in 1972. The term familial hypocalciuric hypercalcemia (FHH) was first used for the same disorder by Marx and coworkers in 1977. Because of its asymptomatic nature, the hypercalcemia may go undiscovered.

Few physicians are familiar with the diagnosis, and appropriate family screening is probably often not done. There may be unnecessary surgical intervention in those cases in which this condition is confused with primary hyperparathyroidism. We present a case of familial hypocalciuric hypercalcemia.

Report of a Case

A 51-year-old woman came for evaluation of persistent hypercalcemia after subtotal parathyroidectomy. A serum calcium level of 10.5 mg per dl (normal 8.5 to 10.5 mg per dl) with a serum phosphorus of 3.2 mg per dl (normal 3.0 to 4.5 mg per dl) had been noted on routine examination in 1975. In April 1977 when she had a hysterectomy, serum calcium was 11.6 mg per dl and serum phosphorus was 2.6 mg per dl. She had had a routine physical examination in Janu-

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ary 1979, at which time her serum calcium was 11.5 mg per dl. Parathyroid hormone (PTH) was reported to be 106 microliter equivalents per ml, with the normal range being 40 to 100 microliter equivalents per ml. Because her half sister had had subtotal parathyroidectomy, workup for multiple endocrine adenomatosis (MEA) was initiated. The results of urinary vanillylmandelic acid (VMA) and serum gastrin concentrations were normal. Intravenous pyelogram was reported within normal limits. At the time of that workup, she did not have symptoms from her hypercalcemia. She underwent subtotal parathyroidectomy in March 1979 at which time she was found to have four parathyroid glands and 3½ were removed. Histologic diagnosis was compatible with parathyroid hyperplasia. Serum calcium levels about a year after her surgery were elevated to 11.2 and 11.4 mg per dl. She continued to be asymptomatic.

Family history. One half sister had had symptoms of fatigue and weight loss. Her serum calcium levels ranged from 11.5 to 12.4 mg per dl. She had had subtotal parathyroidectomy (resection of 3½ parathyroid glands) in December 1975. Hyperplasia was found on microscopic examination of tissue specimen. Five years after her surgical procedure she continues to be hypercalcemic but is asymptomatic. On reviewing her records, her renal calcium to creatinine clearance ratio, based on 24-hour urine studies, was 0.007 and 0.009. Urinary calcium to creatinine clearance ratio in primary hyperparathyroidism is 0.024 ± 0.01 and in familial hypocalciuric hypercalcemia the ratio is 0.006 ± 0.004.

One half brother of the patient has been hypercalcemic for at least five years. He has refused further workup.

The father was the common parent of our patient and her half sister. He died at age 69 of arteriosclerotic disease. The autopsy report noted that two parathyroid glands were seen but were not thought to be remarkable. There was a multinodular goiter weighing about 67 grams with some calcification in its capsule. The record did not contain a serum calcium measurement. There was no notation of enlargement of the pituitary gland, and no tissue sections for histologic examination were obtained. The adrenal glands were not enlarged. There was no adenoma or hyperplasia of pancreatic islets.

One of the patient's sons has serum calcium levels towards the upper limit of normal. Another son and her daughter are normocalcemic. We were unable to discover any other first-degree relatives, either of the patient or of her father.

The patient's physical examination was noncontributory.

Laboratory studies: The patient's serum calcium levels were 11.2 and 12 mg per dl. Twenty-four-hour urinary calcium was low at 90 mg (normal 100 to 700 mg). Computerized tomography (CT) of her chest showed no mediastinal masses suggestive of an ectopic parathyroid gland. Renal calcium to creatinine clearance ratio was calculated to be 0.005. Histologic slides of parathyroid gland were reviewed by our pathologist and hyperplasia of chief cells was diagnosed.

Discussion

Familial benign hypercalcemia was first described by Foley and his group[1] in 1972. The term familial hypocalciuric hypercalcemia was first used for the same disorder by Marx and coworkers[2] in 1977. While studying families of patients with parathyroid hyperplasia, two index patients were found to belong to large kindred groups recognized as having familial hypocalciuric hypercalcemia. They did not show any features of MEA.

In FHH, hypercalcemia shows autosomal dominant transmission with almost 100 percent penetrance at all ages. Hypercalcemia begins at a very early age, that is, before age 10.[2,3]

Most of the patients do not have symptoms. Complications of renal lithiasis and peptic ulcer disease are milder and are seen less frequently than in patients with MEA or typical primary hyperparathyroidism. Twenty-four-hour urinary calcium is much lower, about a third of that seen in typical cases of primary hyperparathyroidism. Urinary calcium excretion is lower in FHH before and after adjustment for differences in creatinine clearance and serum calcium. In FHH, serum magnesium concentration is higher than in the group with primary hyperparathyroidism.[4] Ionized and ultrafiltrable plasma calcium is elevated in patients with FHH and in primary hyperparathyroidism in similar proportions to elevations in total plasma calcium. FHH patients have low urinary calcium to creatinine clearance ratio of less than 0.010 as compared with patients with primary hyperparathyroidism who have a ratio of more than 0.010.[3] Determinations of plasma PTH and cyclic adenosine monophosphate excretion are not helpful in distinguishing patients with FHH from typical primary hyperparathyroid pa-

tients. Histologically, the average amount of parathyroid parenchyma in FHH is 300 percent of that in normal parathyroid glands but considerably less than that in typical primary hyperparathyroidism.[5] Incidence of persistence or recurrence of hypercalcemia is higher in patients with FHH after parathyroidectomy than in typical primary hyperparathyroidism.

As the condition has been recognized only during the last four to five years, the best treatment for these patients remains unclear.[6] The finding of hypocalciuric hypercalcemia in several relatives favors the diagnosis of FHH. In these patients no further surgical treatment for hypercalcemia per se is indicated. The patient described in this report continues to be asymptomatic and her calcium levels have ranged from 11.5 to 12 mg per dl. No surgical intervention was recommended to her. All patients suspected of having primary hyperparathyroidism should routinely have 24-hour urinary calcium test and renal calcium to creatinine clearance ratio determination to rule out FHH. This should be done particularly if the hyperparathyroidism is diagnosed in an asymptomatic patient. If values are consistent with those seen in FHH, then family screening is in order.

REFERENCES

1. Foley TP Jr, Harrison HC, Arnaud CD, et al: Familial benign hypercalcemia. J Pediatr 1972 Dec; 81:1060-1067
2. Marx SJ, Spiegel AM, Brown EM, et al: Family studies in patients with primary parathyroid hyperplasia. Am J Med 1977 May; 62:698-706
3. Marx SJ, Stock JL, Attie MF, et al: Familial hypocalciuric hypercalcemia: Recognition among patients referred after unsuccessful parathyroid exploration. Ann Intern Med 1980 May; 92: 351-356
4. Marx SJ, Spiegel AM, Brown EM, et al: Divalent cation metabolism—Familial hypocalciuric hypercalcemia versus typical primary hyperparathyroidism. Am J Med 1978 Aug; 65:235-242
5. Thorgeirsson U, Costa J, Marx SJ: The parathyroid glands in familial hypocalciuric hypercalcemia. Hum Pathol 1981 Mar; 12:229-237
6. Marx SJ: Familial hypocalciuric hypercalcemia. N Engl J Med 1980 Oct; 303:810-811

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Acute Polyarthritis and Infectious Mononucleosis

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INFECTIOUS MONONUCLEOSIS (IM) is a common illness with protean manifestations ranging from subclinical infection to severe disease affecting many different organ systems. Arthralgias may occur in approximately 5 percent to 10 percent of patients.[1] Well-documented synovitis has rarely been reported. Adebonojo[2] described a 7-year-old girl with infectious mononucleosis in whom an acute inflammatory monarthritis of the ankle joint developed several days after the onset of a sore throat. This report describes an adolescent boy with severe symptoms of IM in whom an acute inflammatory polyarthritis developed.

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Report of a Case

A 16-year-old white boy developed an intensely pruritic, erythematous macular rash over his entire body. Two days later he had complaints of anorexia, fatigue, fever, severe sore throat, swelling of his hands and eyelids and photophobia. He had taken no medications before the onset of the illness. On physical examination his temperature was 38.6°C (101.5°F). There was pronounced injection of the conjunctivae, a fiery red inflammation of the oral mucosa and enlarged inflamed tonsils without exudate. There was mild cervical lymphadenopathy. The liver and spleen were not felt to be enlarged. There was a diffuse macular rash.

Initial laboratory studies showed a leukocyte count of 17,700 per cu mm with a leftward shift. There were only 4 percent lymphocytes, none of which were thought to be atypical. Wintrobe sedimentation rate was 24 mm per hour. Throat culture was negative for beta-hemolytic streptococcus and mononucleosis spot test was positive. Liver function studies were abnormal with moderate elevations in the serum aspartate aminotransferase (formerly serum glutamic oxaloacetic transaminase, SGOT) and serum alanine aminotransferase (formerly serum glutamic pyruvic transaminase, SGPT) and pronounced elevation in the alkaline phosphatase to 429 IU (30 to 100 IU). The lactic dehydrogenase (LDH) and bilirubin determinations were normal and there was no evidence of hepatitis B antigenemia. Complement-fixing antibody titers to herpes simplex,

adenovirus, mumps, cytomegalovirus, influenza and respiratory syncytial virus were each less than 1:8. Epstein-Barr virus (EBV) capsid antibody titer by the indirect fluorescent antibody technique was 1:256.

The patient was admitted to Sequoia Hospital (Redwood City) and begun on a regimen of prednisone, 60 mg daily taken by mouth. He improved rapidly and was discharged from hospital on the fourth day; prednisone administration was stopped three days later. Liver function studies showed improvement but there was not yet a return to normal.

One week after discharge the patient reentered the hospital with complaints of anorexia, fatigue, photophobia and pain in the elbows, wrists and knees. His temperature was 40°C (104°F). On examination he had enlarged lymph nodes and hepatosplenomegaly. Bilateral nummular keratitis had developed.[3] There was tenderness in both temporomandibular joints and in the left shoulder, and swelling and tenderness involving the left wrist, right elbow and fourth proximal interphalangeal joint of the right hand. There was a large effusion in the right knee. Thirty milliliters of cloudy yellow synovial fluid with poor viscosity was aspirated from the right knee. The fluid showed a leukocyte count of 21,000 per cu mm, with 86 percent polymorphonuclear leukocytes and 14 percent mononuclear cells. Gram stain and culture of the fluid were negative for pathogens. Other laboratory results showed a peripheral blood leukocyte count of 14,200 per cu mm with 93 percent polymorphonuclear leukocytes and 7 percent lymphocytes, none of which were atypical. There was persistent mild elevation in liver function studies. Analysis of urine showed no abnormalities. RA latex was negative. Fluorescent antinuclear antibody was present at low titer, 1:20, diffuse, and the C3 complement was moderately elevated. Blood cultures were consistently negative.

Repeat antibody titers for the above-mentioned viruses remained consistently less than 1:8. The EBV antibody titer, however, had increased to 1:2,048. Cryoglobulins were detected in his serum. HLA-B27 antigen was absent. Electrocardiogram showed diffuse ST-segment elevation consistent with acute pericarditis and a liver-spleen scan showed massive hepatosplenomegaly.

Treatment with prednisone was resumed at 60 mg a day. His symptoms lessened and results of laboratory tests returned toward normal ranges. The dose of prednisone was tapered off over a two-month period. He has remained free of rheumatic symptoms after three years of follow-up.

Comments

Rheumatic complaints may accompany several viral infections, most notably rubella, hepatitis B infections, mumps and varicella.[4] Arthralgias and arthritis accompanying infectious mononucleosis have been reported rarely but probably occur more frequently than appreciated.[4] Arthritis accompanying rubella and hepatitis B is thought to be on an immunologic basis resulting from deposition of antigen-antibody complexes in the synovial membrane. Infectious mononucleosis is often associated with increased immune reactivity causing a transient occurrence of various autoantibodies and cryoprecipitates.[5,6] Circulating immune complexes containing EBV antigen and complement components have been detected in patients with urticarial rash complicating infectious mononucleosis.[7] The detection of cryoprecipitates in our patient suggests their possible implication in his acute inflammatory polyarthritis. Unfortunately, analysis of synovial fluid did not include determinations of immune complexes or complement levels.

Our patient had severe disease with high fever and evidence of pericarditis and hepatitis in addition to the polyarthritis. He lacked two of the most characteristic laboratory findings in infectious mononucleosis (that is, lymphocytosis and increased numbers of atypical lymphocytes). Several blood counts actually showed lymphocytopenia. Lymphocytopenic infectious mononucleosis tends to be a more severe clinical illness.[1,8] The diagnosis in our patient was confirmed by both a positive mononucleosis spot test and a substantial rise in the convalescent antibody titer to EBV, a more specific test. Antibody titers to six other viruses showed no rise.

The 7-year-old girl with infectious mononucleosis in the report by Adebonojo had painful swelling of the left ankle, which on aspiration yielded inflammatory synovial fluid and responded within a week to aspirin and bed rest. In a recent review of viral arthritis, three patients with infectious mononucleosis and joint involvement who had not been previously reported were briefly discussed.[9] One had symmetrical involvement of the knees, wrists and small joints of the hands. The second had synovitis of the knees and the third had monarthritis involving a knee. The

synovial fluid was mildly inflammatory and yielded mostly mononuclear cells in two of the three patients.

Recently Pollack and co-workers described a 57-year-old man with heterophil-negative IM who presented with monarthritis of the knee.[10] Arthrocentesis yielded inflammatory synovial fluid with a preponderance of polymorphonuclear leukocytes. The patient was described as being severely ill and lacked atypical lymphocytes, which is similar to our patient.

Most patients with viral arthritis respond to nonsteroidal anti-inflammatory agents. Prednisone had been given to our patient because of the severity of his disease and the extensive organ system involvement. The arthritis responded promptly and completely in seven days.

Recently EBV has been implicated as possibly playing a role in causing rheumatoid arthritis. This stems from observations that patients with rheumatoid arthritis tend to have higher than normal antibody titers to two distinct EBV-associated antigens (rheumatoid arthritis nuclear antigen and Epstein-Barr nuclear antigen) present on EBV-infected lymphoblastoid cells.[11] Thus, EBV may prove to be associated with chronic arthritis.

Summary

Arthralgias occasionally accompany infectious mononucleosis (IM), but the occurrence of unmistakable arthritis is considered rare. We describe a teenaged boy with IM in whom acute inflammatory polyarthritis developed in the course of his disease. The patient had positive heterophilic antibodies but lacked atypical lymphocytes in his blood.

The EBV can thus be responsible for an inflammatory arthritis and should be added to the growing list of viruses known to be associated with this complication. This can be of particular importance in atypical cases of arthritis when the diagnosis of IM is not readily apparent.

REFERENCES

1. Chervenick PA: Infectious mononucleosis. DM, December 1974, pp 1-29

2. Adebonojo FO: Monarticular arthritis: An unusual manifestation of infectious mononucleosis. Clin Pediatr (Phila) 11: 549-550, Sep 1972

3. Pinnolis M, McCulley JP, Urman JD: Nummular keratitis associated with infectious mononucleosis. Am J Ophthalmol 89: 791-794, Jun 1980

4. Hyer FH, Gottlieb NL: Rheumatic disorders associated with viral infection. Semin Arthritis Rheum 8:17-31, Aug 1978

5. Sutton RNP, Emond RTD, Thomas DB, et al: The occurrence of autoantibodies in infectious mononucleosis. Clin Exp Immunol 17:427-436, Jul 1974

6. Kaplan ME: Cryoglobulinemia in infectious mononucleosis: Quantitation and characterization of the cryoproteins. J Lab Clin Med 71:754-765, May 1968

7. Wands JR, Perrotto JL, Isselbacher KJ: Circulating immune complexes and complement sequence activation in infectious mononucleosis. Am J Med 60:269-272, Feb 1976

8. Bar RS, Adlard J, Thomas FB: Lymphopenic infectious mononucleosis. Arch Intern Med 135:334-337, Feb 1975

9. Sauter SVH, Utsinger PD: Viral arthritis. Clin Rheum Dis 4:225-240, 1978

10. Pollack S, Enat R, Barzilai D: Monoarthritis with heterophil-negative infectious mononucleosis—Case of an older patient. Arch Intern Med 140:1109-1111, Aug 1980

11. Catalano MA, Carson DA, Slovin SF, et al: Antibodies to Epstein-Barr virus-determined antigens in normal subjects and in patients with seropositive rheumatoid arthritis. Proc Natl Acad Sci USA 76:5825-5828, Nov 1979

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Postoperative Infection of an Aortic Prosthesis With *Achromobacter xylosoxidans*

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Achromobacter xylosoxidans is a Gram-negative bacillus that is motile (with peritrichous flagellae), nonfermentive and capable of catabolizing xylose but not lactose, maltose, mannitol or sucrose. It was originally isolated from human ear discharge specimens in 1971[1] and has been found in specimens from several other sites, including ventricular cerebrospinal fluid (CSF), pleural fluid, peritoneal fluid, urine, feces and swabs of the eye, ear and pharynx.[2] The natural habitat of *A xylosoxidans* is not known, but it may be a water bacterium, having been isolated from a swimming pool.[3] It has also been implicated in nosocomial infections by isolation from chlorhexidine solutions.[4] We report the case of a patient with infection of an aortic vascular prosthesis caused by *A xylosoxidans* to record the extent of pathogenicity of this microorganism. At the same time, this case shows the difficulty of achieving bactericidal therapy and chronicles the suppression

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of infection in a Dacron vascular graft without removal of the device or cure of the infection by prolonged outpatient treatment with antimicrobics.

Report of a Case

A 35-year-old white man was referred to the University of California Davis Medical Center (UCDMC) on May 5, 1978, for evaluation and treatment of dissection of the aortic root just above the aortic valve, with extension to the left of the subclavian artery, and resultant aortic stenosis and aortic insufficiency. On June 5, 1978, the ascending and transverse aorta was resected, a 30-mm low-porosity Dacron tube graft inserted, the arterial supply to the head implanted and the aortic valve replaced with a #29 Hancock porcine prosthesis. The postoperative course was benign and the patient returned to duty as a law enforcement officer. Six months later he noted fever, malaise, myalgias and pain in the shoulder and arm that was distinct from the pain of his aortic dissection. He had a fullness in his suprasternal notch. Cardiac catheterization in February 1979 showed good function of the graft and valve. Four blood cultures were sterile. Symptomatic improvement followed administration of cephalothin sodium, but low-grade fever continued after discharge. The fullness of the suprasternal notch persisted until April 1979, when pus drained spontaneously from it.

TABLE 1.—*Results of Susceptibility Testing In Vitro of* Achromobacter xylosoxidans *Using a Tube-Dilution Method*

Antimicrobial Drugs	*Minimal Inhibitory Concentration µg/ml*	*Minimal Lethal Concentration µg/ml*
Ampicillin	16/32	>128
Cephalothin	>128	
Carbenicillin	≤ 8	>512
Tetracycline	> 32	
Chloramphenicol	16	
Nitrofurantoin	R*	
Trimethoprim/ sulfamethoxazole	0.25/5.0	>8/160
Gentamicin	> 12	
Tobramycin	> 12	
Amikacin	> 64	
Cycloserine	128 (>256)	>128 (>256)
Ticarcillin	16	512
Rifampin	16	> 64
Cefoxitin	>128	>128
Cefamandole	16	>128
Moxalactam	4	>512
Piperacillin	4	>128
Mezlocillin	4	>256
Azlocillin	1	>256
Cefotaxime	128	>256
Neomycin	64	128
Spectinomycin	>256	>256
Streptomycin	256	>256
d-Alanine	>128	>128
Thienamycin	32	>128
Bacitracin	> 64	> 64
Netilmicin	> 16	> 16

*R = resistant

In admission to UCDMC on May 7, 1979, a sinogram on that day showed a tract communicating with the mediastinum; the contrast material collected around the aortic graft. A blood culture done before admission to hospital yielded *Achromobacter xylosoxidans* with susceptibilities in vitro as shown in Table 1. On May 10 treatment was begun with carbenicillin (400 mg per kg of body weight per day as six equal portions injected intravenously every 4 hours), trimethoprim-sulfamethoxazole (two tablets [320 mg plus 1,600 mg] every 12 hours) and rifampin (8 mg per kg of body weight per day as two equal portions taken by mouth every 12 hours). Fever continued, rising to 40.2°C (104.7°F); the carbenicillin was discontinued, and moxalactam (80 mg per kg of body weight per day as three equal portions given intravenously every 8 hours) was substituted on May 16. He was afebrile throughout the rest of his hospital course although the drug levels in serum obtained at the time of maximal concentrations of antimicrobics were not lethal for the patient's *A xylosoxidans* at 1:2 dilution, the lowest tested. The erythrocyte sedimentation rate (ESR) fell from 57 mm per hour on admission to 38 mm per hour on June 14. Cultures of blood specimens taken on May 14, May 29, June 4 and June 14 were sterile. He was discharged and continued as an outpatient on the same regimen of moxalactam, trimethoprim-sulfamethoxazole and rifampin. Although clinical improvement continued and the ESR fell even further, blood cultures persisted positive (Table 2).

On June 25, the dose of moxalactam was doubled to 160 mg per kg of body weight per day as three equal portions given intravenously every eight hours via a Hickman catheter (inserted in the right cephalic vein on June 19, 1979). Because blood cultures continued positive, on August 30 the dosage of rifampin was increased to 12 mg per kg of body weight per day as three equal portions taken by mouth every eight hours, and on October 11 the dosage of trimethoprim-sulfamethoxazole was increased to two tablets every eight hours. The ESR had returned to normal by September 20 and remained <10 mm per

hour throughout the rest of his treatment. The patient was active and felt well but blood cultures continued to yield *A xylosoxidans* (Table 2); both moxalactam and trimethoprim-sulfamethoxazole were discontinued on November 19, 1979.

Treatment with azlocillin (300 mg per kg of body weight per day as four equal portions given intravenously every six hours) was started on November 20. At the same time, the rifampin dosage was increased to 15 mg per kg of body weight per day as four equal portions taken by mouth every six hours. Blood cultures obtained after instituting treatment with azlocillin plus rifampin were sterile. On January 2, 1980, severe pruritis and a general maculopapular, erythematous, crusting rash in the flexor creases developed. On January 9 prednisone treatment was initiated after antihistamines were unsuccessful at ameliorating his symptoms. With the addition of trimeprazine tartrate, the rash and pruritis were controlled. The dosage of azlocillin was decreased to 250 mg per kg of body weight per day (as four equal portions given intravenously every six hours) for the last five weeks of treatment—terminated at the request of the patient on March 3, 1980 after 15 weeks of azlocillin-rifampin.

About four weeks after the antimicrobial drugs were discontinued, fevers, chills, sweats and malaise recurred. A mass appeared in the suprasternal notch and was incised, with removal of granulation tissue and suture material on April 25, 1980; azlocillin was given perioperatively. The surgical specimen yielded *A xylosoxidans,* but blood cultures perioperatively were sterile. About a month later, bacteremia was again documented. After azlocillin-rifampin treatment was begun (adverse reaction to the azlocillin was controlled by giving thalidomide) bacteremia ceased, although malaise and periods of low-grade fever were recurrent. Cultures of the suprasternal sinus tract continued to yield *A xylosoxidans* and a sinogram on October 7, 1980, showed communication with the mediastinum and collection of the contrast medium around the aortic prosthesis.

Although azlocillin-rifampin treatment was continued, bacteremia recurred in February 1981 and was associated with fever and malaise. Increasing the dose of azlocillin and eventually re-

TABLE 2.—*Correlation of Blood Culture Results With Antimicrobial Therapy*

Date	*Blood Cultures**	*Treatment†*
05/03/79	3 sets *Achromobacter xylosoxidans*	.....
05/08/79	2 sets *A xylosoxidans*	.....
05/10/79	.....	Carbenicillin, trimethoprim/sulfamethoxazole and rifampin started
05/14/79	2 sets sterile	.....
05/16/79	.....	Carbenicillin discontinued. Moxalactam started
05/29/79	2 sets sterile	.....
06/04/79	2 sets sterile	.....
06/14/79	2 sets sterile	.....
06/25/79	2 sets sterile	Moxalactam dose increased
07/05/79	1 of 2 sets *A xylosoxidans*	.....
07/12/79	2 sets sterile	.....
07/19/79	1 set sterile	.....
08/02/79	2 sets sterile	.....
08/16/79	1 of 2 sets *A xylosoxidans*	.....
08/30/79	.....	Rifampin dose increased
09/29/79	2 of 2 sets *A xylosoxidans*	.....
10/11/79	1 of 2 sets *A xylosoxidans*	Trimethoprim-sulfamethoxazole increased
11/20/79	.....	Azlocillin substituted for moxalactam. Trimethoprim-sulfamethoxazole stopped. Rifampin increased.
11/29/79	2 of 2 sets sterile	.....
12/13/79	2 of 2 sets sterile	.....
01/08/80	2 of 2 sets sterile	.....
01/09/80	.....	Prednisone therapy started for pruritis and rash. Trimeprazine added.
01/17/80	2 of 2 sets sterile	.....
01/24/80	.....	Azlocillin decreased
01/31/80	2 of 2 sets sterile	.....
03/03/80	.....	Therapy discontinued
03/06/80	2 of 2 sets sterile	.....
03/13/80	2 of 2 sets sterile	.....

*One set consists of one bottle of Columbia broth and one bottle of Trypticase-soy broth.
†See text for dosages.

TABLE 3.—*Results of Assessment in Vitro of Two-Drug Combinations for Possible Synergy*

Two-drug Combinations	*Results*
Moxalactam + CP-45-899*	No synergy
Ticarcillin + CP-45-899*	No synergy
Trimethoprim + sulfamethoxazole	No synergy
Moxalactam + rifampin	No synergy
Ticarcillin + rifampin	No synergy
Cycloserine + moxalactam	Possible antagonism
Moxalactam + streptomycin	Possible additive effect
Netilmicin + carbenicillin	No synergy
Azlocillin + rifampin	Synergy present

*A competitive inhibitor of β-lactamases.

placing the rifampin with co-trimoxazole failed to eliminate the bacteremia despite the finding by in vitro testing of serum bactericidal titers as high as 1:64 against the patient's current *A xylosoxidans*. Surgical therapy was advised. However, a major cerebral embolus precluded operation and the patient died on October 19, 1981.

Discussion

Achromobacter xylosoxidans is uncommonly pathogenic, though there is some question as to whether the true prevalence of this organism is really known. Confusion with *Pseudomonas* sp may occur if the flagellar arrangement is not defined. However, some authors[5] feel that the colonial morphology and the pattern of susceptibility to antimicrobial drugs may help differentiate *A xylosoxidans* from other nonfermenting, oxidase-positive, Gram-negative bacilli. Many isolates from clinical specimens were obtained from surface cultures of ears, sputum or urine; often, several other kinds of microorganisms were isolated from the same specimen.

The few reports of antimicrobial susceptibility studies[1-7] provide little hope for success with conventional antibacterial agents. Because of the foreign body in our patient, the difficulty in finding a clinically achievable minimal lethal concentration (see Table 1) and the persistently positive blood cultures, we instituted an extensive search for a combination of antimicrobial drugs that would act synergistically (Table 3). Azlocillin plus rifampin appeared suitable by in vitro testing, and when applied in therapy yielded a peak serum bactericidal titer of 1:8. Concurrently, the blood cultures became sterile and remained sterile after discontinuation of therapy. The choice of length of therapy was arbitrary as guidelines for the treatment of chronic intravascular infections, especially in the presence of foreign bodies, are not available. This patient received intravenous infusions every eight hours as an outpatient for six months without either secondary infection or difficulties of venous access.

The conventional treatment of infections involving vascular prostheses is based on removing the foreign body along with appropriate antimicrobial therapy.[8] Though there are poorly documented reports of cures with nonsurgical management, there are many more reports of catastrophes in patients treated in this manner.[9-12] It was not technically feasible to remove the Dacron aortic graft from our patient.

We regard the infection as being perioperative, even though the patient did not develop symptoms until six months after the surgical procedure. Some experimental work in dogs has shown that vascular prostheses are susceptible to infection for at least four months after being implanted though the risk of infection decreases over that period.[13] In previous studies of large series of patients with infected vascular prostheses, the mean elapsed time from operation to clinical manifestations of infection when prophylactic antimicrobial drugs were used in the perioperative period was 11.5 months.[8,12]

The development of severe hypersensitivity during therapy posed an additional problem in the management of our patient. Through the use of antihistamines, and topical and systemic administration of glucosteroids, it was possible to continue therapy for eight weeks after allergic reaction became evident.

A xylosoxidans can cause severe clinical infections when there is a defect in host defenses. Such infections are difficult to treat because *A xylosoxidans* is resistant to many antimicrobial drugs. Suppressive therapy may depend on the long-term application of bactericidal antimicrobial drugs. It is very difficult, if not impossible, to eradicate infections in vascular prostheses without removal despite long-term bactericidal antimicrobial therapy.

REFERENCES

1. Yabuuchi E, Oyama A: *Achromobacter xylosoxidans* n. sp. from human ear discharge. Jpn J Microbiol 15:477-481, Sep 1971

2. Igra-Siegman Y, Chmel H, Cobbs C: Clinical and laboratory characteristics of *Achromobacter xylosoxidans* infection. J Clin Microbiol 11:141-145, Feb 1980

3. Holmes B, Snell JJS, Lapage SP: Strains of *Achromobacter xylosoxidans* from clinical material. J Clin Pathol 30:595-601, 1977

4. Shigeta S, Yasunaga Y, Honzumi K, et al: Cerebral ventriculitis associated with *Archromobacter xylosoxidans*. J Clin Pathol 31:156-161, Feb 1978

5. Pien FD, Higa HY: *Achromobacter xylosoxidans* isolates in Hawaii. J Clin Microbiol 7:239-241, 1978

6. Yabuuchi E, Yano I, Goto S, et al: Description of *Achromobacter xylosoxidans* Yabuuchi and Oyama 1971. In J System Bacteriol 24:470-477, 1974

7. Dworzack DL, Murray CM, Hodges GR, et al: Community-acquired bacteremic *Achromobacter xylosoxidans* type IIIa pneumonia in a patient with idiopathic IgM deficiency. Am J Clin Pathol 70:712-717, Oct 1978

8. Goldstone J, Moore WS: Infection in vascular prostheses—Clinical manifestations and surgical management. Am J Surg 128:225-233, Aug 1974

9. Szilagyi EM, Smith RF, Elliott JP, et al: Infection in arterial reconstruction with synthetic grafts. Ann Surg 176:321-333, 1972

10. Conn JH, Hardy JD, Chavez CM, et al: Infected arterial grafts: Experience in 22 cases with emphasis on unusual bacteria and techniques. Ann Surg 171:704-713, 1970

11. Hoffert PW, Gensler S, Haimovici H: Infection complicating arterial grafts. Arch Surg 90:427-435, 1965

12. Fry WJ, Lindenauer SM: Infection complicating the use of plastic arterial implants. Arch Surg 94:600-609, 1967

13. Swanson RJ, Moore WS, Campagna G: Effect of time on vascular protheses' susceptibility to infection of bacteremic origin. Surg Forum 24:28-29, 1973

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The Malignant Potential of Mucinous Cysts of the Pancreas

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CYSTIC LESIONS of the pancreas are relatively uncommon. The most frequently encountered cystic lesion is the inflammatory pseudocyst, usually in association with pancreatitis or trauma. Less common, true cysts of the pancreas have been categorized as retention, congenital, and neoplastic or proliferative cysts.[1]

Approximate frequency distributions of pancreatic cysts quoted in various articles are: pseudocyst, 70 percent to 75 percent; retention, 10 percent; congenital, 2 percent to 3 percent, and neoplastic, 10 percent to 15 percent (Table 1).[2-5] The latter category includes benign nonmucinous glycogen-rich adenomas (formerly called serous cystadenoma) and mucinous cystic neoplasms (potentially malignant mucinous cystadenoma and overtly malignant cystadenocarcinoma). Neoplastic cysts are divided nearly equally into microcystic adenomas, mucinous cystadenomas and cystadenocarcinomas. Of all primary pancreatic malignant lesions, cystadenocarcinoma makes up only about 1 percent.[4]

ABBREVIATIONS USED IN TEXT

CAT = Computerized axial tomography
ERCP = endoscopic retrograde cholangiopancreatography

TABLE 1.—*Approximate Frequency Distribution of Pancreatic Cysts. (Rentention, Congenital and Neoplastic Cysts All Have Epithelial Linings)*

Pancreatic Cysts	*Frequency of Occurrence (%)*
Pseudocyst	70-75
Retention cyst	10
Congenital cyst	2- 3
Neoplastic cyst	10-15
Microcystic adenoma	
Mucinous cystadenoma	
Cystadenocarcinoma	

Adequate treatment of these lesions, which first requires accurate diagnosis, is especially critical for the neoplastic cysts; the established treatment for the mucinous cystic neoplasms is total excision whether or not unmistakable malignancy is observed on biopsy.[2-4,6] The point is reemphasized in the present case, in which a relatively unusual pleomorphic adenocarcinoma appeared after 12 years in a mucinous cystic neoplasm originally considered to be a traumatic pseudocyst.

Report of a Case

In July 1979 a 35-year-old woman was transferred to University of California, Los Angeles (UCLA) Hospital from a local community hospital for evaluation and treatment of a rapidly enlarging epigastric mass. She was first seen at her local hospital in 1964 at age 20 after suffering lower extremity fractures when her car backed into her in the driveway. She said there was no abdominal trauma. Three years later a left subcostal mass developed which at exploratory laparotomy was reported to be a 16-cm pseudocyst of the tail of the pancreas. The cyst contained straw-colored fluid and was thought to be traumatic in origin, despite her denial of abdominal trauma. The rest of the pancreas was noted to be soft and normal appearing though a "little lobulated." A biopsy of the cyst wall was reported to show "occasional

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gland-like structures having a simple columnar epithelium," without evidence of malignancy. A cystogastrostomy was carried out.

The patient remained well for the next ten years, but early in 1977 she noted increasing pressure and swelling in her left epigastrium resembling her symptomatology in 1967. Upper gastrointestinal series showed anterior displacement of the stomach and apparent recurrent anterior pancreatic cyst; serum amylase at that time was 81 units per dl (normal to 130 units per dl). During a surgical procedure done in May 1977, several cysts were found in the tail of the pancreas, the largest two containing 800 ml and 400 ml of murky dark fluid, and the two smallest containing 50 ml and 5 ml of fairly clear, slightly yellow-tinged serous mucus. The remainder of the pancreas was reported to be lobulated and small. A pancreatocystogastrostomy was again done but no biopsy specimen was taken.

A month later the patient began experiencing left upper quadrant fullness with fever and chills. An external drainage procedure was unsuccessful and she underwent a more extensive procedure in July 1977, including marsupialization of five large pancreatic cysts, drainage of a lesser sac abscess and takedown of the previous cystogastrostomy. She recovered from this procedure satisfactorily. A biopsy specimen of the cyst wall taken during that operation is described below.

The patient was asymptomatic for two years until June 1979, when she noted the onset of increasing epigastric fullness with symptoms of nausea, vomiting, anorexia, malaise, abdominal discomfort and an 8-kg (18-lb) weight loss over a six-week period. An ultrasound scan in July 1979 showed a 4- by 5-cm epigastric cystic mass with a dense 7-cm mass posteriorly; upper gastrointestinal series showed pronounced anterior displacement of the stomach. The following week symptoms of increasing epigastric fullness and discomfort prompted surgical intervention, during which an ulcer was found in the posterior wall of the stomach with a retrogastric mass from which no fluid could be aspirated. Through the posterior wall of the stomach, a biopsy specimen of an extensive fleshy mass was taken, shown by frozen section to be a highly undifferentiated neoplasm compatible with pancreatic carcinoma. The incision was closed and after permanent histologic sections confirmed the diagnosis, the patient was referred to UCLA Hospital several days later for a more definitive procedure.

Abdominal arteriography and computerized axial tomography (CAT) were done to define the extent of tumor spread and to aid in determining resectability. Although findings of both studies indicated a large pancreatic mass, it appeared to be discrete from surrounding structures and possibly resectable. Shortly thereafter surgical exploration was carried out through an extensive left thoracoabdominal incision. Considerable careful dissection was required to free the large pancreatic tumor from adjacent retroperitoneal structures, closely adherent superior mesenteric and portal veins, transverse mesocolon, duodenum and liver. The stomach was invaded by the tumor mass and removal of the tumor required a 95-percent gastric resection, 85-percent pancreatic resection of body and tail, splenectomy and Roux-en-Y gastrojejunostomy. The procedure was satisfactorily tolerated by the patient, with an estimated blood loss and whole-blood replacement of approximately 5 liters.

Histologic Findings

The biopsy slide from the original cyst wall (1967) was reviewed and found to contain mucinous glands embedded in a cellular stroma resembling that of the ovary. Although the epithelium was not well oriented, a few mucinous cells were seen (Figure 1a). Tissue specimens were not taken from the second or third operation (May and June 1977). A review of the biopsy from the fourth operation (July 1977) showed the cyst wall to be composed of dense collagenous fibrous tissue with scattered chronic inflammatory cells and a few mucinous glands. The surface was covered with fibrin and only a few disrupted mucinous epithelial remnants were found (Figure 1b). Both the 1967 and 1977 specimens contained features of a mucinous cystic neoplasm without evidence of malignancy.

The 1979 resected specimen consisted of distal stomach, proximal duodenum and pancreas, the latter almost completely replaced by a tumor that ulcerated the posterior wall of the stomach, creating an 8-cm defect in the mucosa. The tumor was lobular, measuring 17 by 15 by 10 cm and weighing 2 kg. It was predominantly solid with multilocular cystic areas containing mucinous cysts measuring up to 3 cm in diameter (Figure 2); the solid area was gray and yellow with fibrous septae.

Histologically the tumor showed epithelial cells loosely arranged, with occasional spindled areas and rare attempts at gland formation. The cells were pleomorphic with hyperchromatic nuclei,

numerous mitotic figures and granular cytoplasm (Figure 3a); multinucleated cells were frequent. Staining with mucicarmine showed cytoplasmic mucin and electron microscopy disclosed features of a poorly differentiated carcinoma. Sections of the cystic areas revealed a mucinous lining with occasional papillary infoldings (Figure 3b). No notable atypia of the glandular epithelium was seen; however, foci of direct communication of the epithelium into necrotic tumor were observed. Two of nine adjacent lymph nodes contained metastatic tumor.

Postoperative Course

The patient recuperated reasonably well in the immediate postoperative period, and by the eighth day was taking clear liquids. She was discharged on the 14th day with wounds healing well, drains removed and no palpable mass. However, 3½ weeks later she was admitted to her local hospital with the complaint of recurrent epigastric fullness and anorexia; upon transfer to UCLA Hospital she was found to have an epigastric mass fully as large as the previous one. A CAT scan and abdominal ultrasonography confirmed that a large mass had recurred in the region of the pancreas; liver-spleen scan showed multiple large filling defects in the liver. In view of the aggressiveness of the tumor

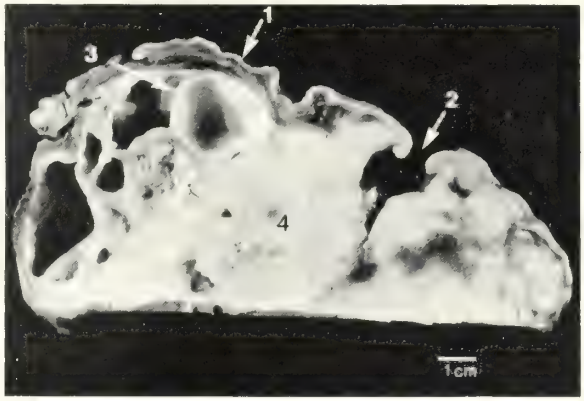

Figure 2.—A cross section of the gross specimen showing gastric mucosa on the surface **(1)** along with the ulcerated area **(2)**. The tumor is cystic **(3)** and solid **(4)**.

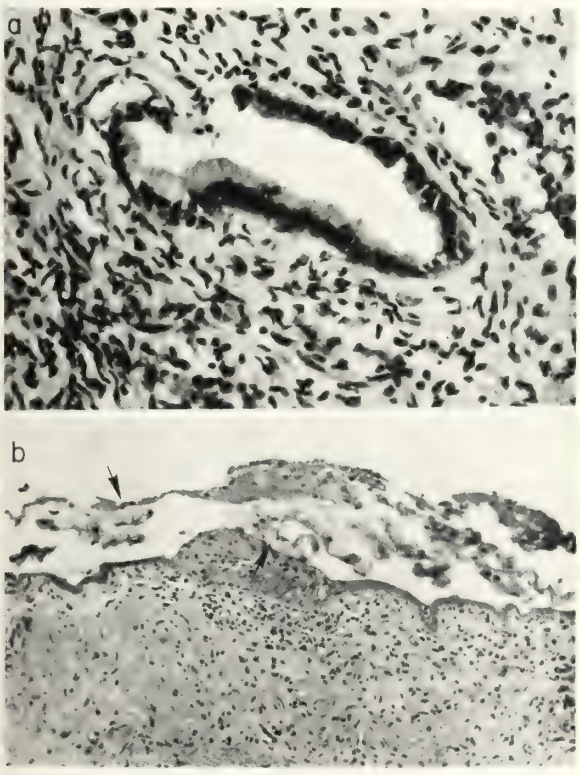

Figure 1.—**(a)** A mucinous gland from the original cyst wall biopsy (1967) embedded in a cellular stroma resembling that of the ovary. (Hematoxylin-eosin-stained tissue section, reduced from magnification × 300.) **(b)** A section of the cyst wall from the fourth operation (July, 1977). Note the residual mucinous epithelium **(arrows)**. (Hematoxylin-eosin stain, reduced from magnification × 100.)

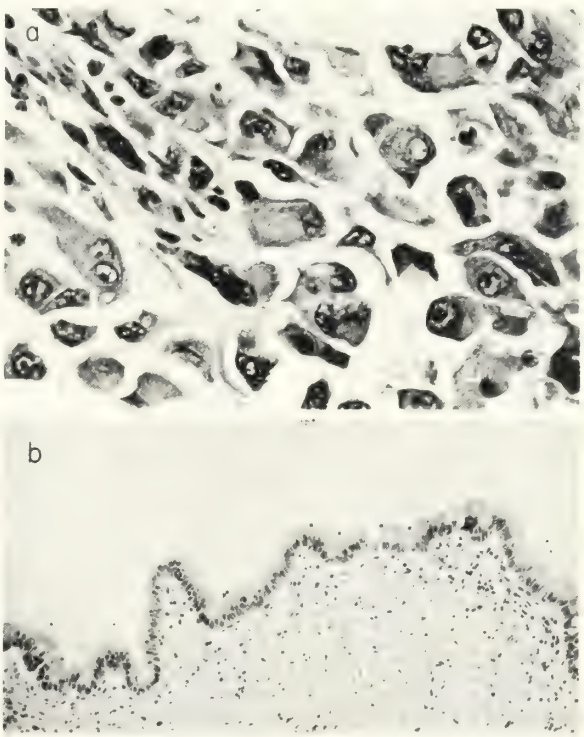

Figure 3.—**(a)** A representative section of the solid portion of the tumor showing the pleomorphic, sarcoma-like pattern. (Hematoxylin-eosin stain, reduced from magnification × 600.) **(b)** A section through one of the cystic areas showing benign mucinous epithelium. (Hematoxylin-eosin stain, reduced from magnification × 150.)

no further therapy was given. She was returned to her local hospital where she died a few days later.

Discussion

Cystic neoplasms of the pancreas have been categorized into two major groups: nonmucinous glycogen-rich microcystic adenomas[5] and mucinous cystic neoplasms.[6] The first group, which has no malignant potential, is thought to arise from the acinar wall; these adenomas were formerly called serous or centroacinar cystadenomas. The second category, the mucinous cystic adenomas, arises from ductal epithelium and comprises the premalignant mucinous cystadenomas (also tall columnar or papillary cystadenomas) and the malignant cystadenocarcinomas. Compagno and Oertel[5,6] clearly distinguish the microcystic adenomas, which have never been shown to develop into malignancy, from the mucinous cystic neoplasms that form a continuum with latent to overt malignancy. Transformation from a benign to a malignant mucinous cystic neoplasm is described in the present case and also in a 1960 report by Probstein.[7] Both cases were progressive over 12 and 10 years, respectively. Others in the past have suggested this malignant potential, based primarily on the finding of both histologically malignant and benign-appearing areas in the same tumor.[8-10]

In the case described here, the tumor began as a large mucinous cyst in the tail of the pancreas in a young (then 23-year-old) woman and had an ovarian-like stroma, characteristic of a mucinous cystic neoplasm.[6] The lesion recurred several times, and though it was drained by various means, excision was never attempted until it became malignant. The malignant transformation of mucinous cystic neoplasms is usually into a well-differentiated cystadenocarcinoma,[6] and these neoplasms generally have a better prognosis than the typical duct cell adenocarcinoma.[11] This case shows a poorly differentiated variant with a worse prognosis and resembles the entity described in various terms such as *pleomorphic adenocarcinoma,*[12,13] *pleomorphic carcinoma,*[14-17] *sarcomatoid carcinoma,*[18] *giant cell carcinoma,*[11,19] and *carcinosarcoma.*[20] We prefer the term pleomorphic adenocarcinoma because the pattern bears some resemblance to a pleomorphic rhabdomyosarcoma. This term also distinguishes it from the *giant cell carcinoma, epulis type.*[11,19,21] Grosfeld and colleagues[22] reported a similar case of sarcomatous degeneration preceded by a mucinous cystadenoma; others noted the pleomorphic pattern as a focal change in a mucinous cystadenocarcinoma.[6,15,20] The poorer prognosis is undoubtedly due to the higher grade of the neoplasm.

Clinical Features of Differential Diagnosis

This case reemphasizes the need to differentiate mucinous cystic neoplasms of the pancreas from all other benign pancreatic cysts. Differentiation from the more prevalent pseudocyst is easily made on the basis of the clinical history, since pancreatitis usually precedes pseudocyst formation as a result of alcohol abuse, trauma or cholelithiasis. On the other hand, pancreatic mucinous cystic neoplasms have an insidious onset, many first discovered as a palpable upper abdominal mass, with the cyst diameter often greater than 10 cm at time of diagnosis.[2] Mucinous cystic neoplasms are three to nine times more frequent in females;[2,3,23] 95 percent arise in the pancreatic body and tail and are typically slow growing. Pain in the epigastrium or left upper quadrant is the most frequent symptom (50 percent to 80 percent);[2,3,6] other complaints are usually caused by pressure on contiguous organs. Jaundice has been occasionally reported in the few cases where the cyst occurs in the head of the pancreas, but pancreatitis is almost never implicated. Associated biliary disease has been reported in 12 percent to 27 percent of the patients with pancreatic mucinous cystic neoplasms[2,3] and diabetes mellitus in 8 percent to 17 percent.[2,6,24]

Two aspects of congenital and retention cysts aid in differentiation: (1) the former are usually solitary whereas mucinous cystic neoplasms tend to be multiloculated, and (2) retention cysts characteristically follow trauma.

In this case the patient's earlier involvement in an automobile accident may at first have misled the operating surgeons.

Radiologic Features of Differential Diagnosis

The preoperative diagnosis of mucinous cystic neoplasm is not always straightforward; Compagno[6] pointed out that in the 41 cases he reviewed, the most common preoperative clinical diagnosis was pancreatic pseudocyst. Traditional radiographic features of cystic pancreatic neoplasms tended to be nonspecific before the first description of the angiographic appearance of cystadenoma in 1957.[25] Barium upper gastrointestinal series, the most common study, has a 50 percent to 90 percent success rate in showing a retrogastric mass,[2,4,10] whereas intravenous pyel-

ography and barium enema studies show caudad displacements of the left kidney in 66 percent of the cases and splenic flexure of the colon in 50 percent.[2] The classic "sunburst" pattern of calcification is seen in less than 10 percent of cystic neoplasms, while chronic pancreatitis can show typical small calcifications and a pseudocyst wall can evidence curvilinear calcifications.[23]

In recent years new technical developments in roentgenography, particularly angiography, ultrasonography, computerized axial tomography and, on occasion, endoscopic retrograde cholangiopancreatography (ERCP) have helped in differentiating cystic neoplasms from other pancreatic cysts. On angiography, cystic neoplasms tend to appear hypervascular with enlarged feeding arteries, neovascularity and characteristic tumor stain.[23] The degree of vascularity is related to the relative proportion of cystic to solid tumor, and some have been reported to be hypovascular. A malignant neoplasm cannot be determined by angiography alone unless metastasis or invasion of adjacent organs is demonstrated.

Combining ultrasound with angiography will further define a cystic lesion, and in particular helps to differentiate a hypovascular cystic tumor from a pseudocyst.[23,26,27] Several recent reports have shown that the use of CAT scans improves the ability to diagnose pancreatic cystic neoplasms.[26,28] Moreover, for pseudocysts, ERCP will fill 60 percent and will usually show the typical ductal changes of pancreatitis, which may be helpful on occasion.[23]

Treatment

Definitive diagnosis is achieved by doing exploratory laparotomy and biopsy of the pancreatic cystic lesion. It has been suggested by ReMine[3] in a discussion of pancreatic cystadenoma that in the absence of a history of pancreatitis one should expect the cyst to be either cystadenoma or cystadenocarcinoma. Frey[29] advises that biopsy should be routinely obtained in all cases of pancreatic pseudocysts to rule out unsuspected cystadenocarcinoma and McCune, in his discussion of Becker, Welsh and Pratt's paper,[2] recommends the same for any pancreatic cyst. Because of its malignant potential, any mucinous cystic neoplasm found on biopsy should be totally excised, if possible, whether or not it is found to be malignant histologically. The nonmucinous microcystic adenomas need not be totally excised since none have ever been shown to undergo malignant transformation. Total excision of a mucinous cystic neoplasm should be done at the time of initial surgical exploration or soon thereafter when the diagnosis is confirmed. One patient with initially unrecognized mucinous cystic neoplasm underwent an internal drainage that was removed five years later and the cyst resected.[3] Since the tumors grow slowly and metastasize late, even large cystadenocarcinomas are often resectable. However, for unresectable tumors Becker and co-workers[2] have indicated that internal drainage might give transient relief if the lesions are predominantly cystic, and Piper and colleagues[30] have suggested that initial decompression might in rare cases be followed by successful total excision. Marsupialization is not recommended,[2,3] though one reported "cure" exists, perhaps of a benign microcystic adenoma.[3,30] In the present case there were several opportunities (1967, 1977) to excise the mucinous cystic neoplasm before it underwent degeneration.

Prognosis for cystadenocarcinoma is generally better than for other pancreatic carcinomas, if totally excised before invasion of adjacent structures, and Hodgkinson and co-workers[1] have shown a 64-percent five-year survival rate for these patients. Pleomorphic adenocarcinoma as seen in this patient has a much worse prognosis than cystadenocarcinoma, with median survival between three and seven months in various series,[13,16] which is substantially the same as for the typical duct cell adenocarcinoma.[11] There is one reported case of a patient surviving for five years with pleomorphic adenocarcinoma after total pancreatectomy.[17]

Summary

A pleomorphic adenocarcinoma arising in a long-standing mucinous cystic neoplasm of the pancreas was found in a 35-year-old woman. She had a 12-year history of recurrent pancreatic cysts—initially considered to be traumatically caused—which were drained internally by cystogastrostomy on several occasions. The malignant potential of mucinous cystic neoplasms (mucinous cystadenoma or tall columnar cystadenoma) of the pancreas demands adequate tissue sampling of all cystic lesions of the pancreas at time of laparotomy. It is imperative to differentiate these premalignant cysts from other truly benign pancreatic cysts (nonmucinous glycogen-rich microcystic adenomas, retention and congenital pancreatic cysts, and common inflammatory pseudocysts) inasmuch as complete excision is the preferred treatment for

any mucinous cystic neoplasm whether or not definite malignancy is seen. This case reemphasizes the importance of adequate biopsy and histopathologic evaluation of all cystic lesions of the pancreas, regardless of the clinical presentation.

REFERENCES

1. Mayo-Robson AW, Moynihan BG: Diseases of the Pancreas. Philadelphia, WB Saunders Co, 1903

2. Becker WF, Welsh RA, Pratt HS: Cystadenoma and cystadenocarcinoma of the pancreas. Ann Surg 161:845-863, Jun 1965

3. Hodgkinson DJ, ReMine WH, Weiland LH: Pancreatic cystadenoma—A clinicopathologic study of 45 cases. Arch Surg 113: 512-519, Apr 1978

4. Hodgkinson DJ, ReMine WH, Weiland LH: A clinicopathologic study of 21 cases of pancreatic cystadenocarcinoma. Ann Surg 188:679-684, Nov 1978

5. Compagno J, Oertel JE: Microcystic adenomas of the pancreas (gylcogen-rich cystadenomas): A clinicopathologic study of 34 cases. Am J Clin Pathol 69:289-298, Mar 1978

6. Compagno J, Oertel JE: Mucinous cystic neoplasms of the pancreas with overt and latent malignancy (cystadenocarcinoma and cystadenoma)—A clinicopathologic study of 41 cases. Am J Clin Pathol 69:573-580, Jun 1978

7. Probstein JG, Blumenthal HT: Progressive malignant degeneration of a cystadenoma of the pancreas. Arch Surg 81:683-689, Nov 1960

8. Lichtenstein L: Papillary cystadenocarcinoma of the pancreas. Am J Cancer 21:542-553, Jul 1934

9. Sawyer KC, Spencer JR, Lubchenco AE: Proliferation cysts of the pancreas. Ann Surg 135:549-554, Apr 1952

10. Warren KW, Hardy KG: Cystadenocarcinoma of the pancreas. Surg Gynecol Obstet 127:734-736, Oct 1968

11. Cubilla AL, Fitzgerald PJ: Pancreas cancer—I. Duct adenocarcinoma—A clinical-pathologic of 380 patients. Pathol Annu 13:241-289, 1978

12. Guillan RA: Pleomorphic adenocarcinoma of the pancreas—An analysis of five cases. Cancer 21:1073-1079, Jun 1968

13. Guillan RA, McMahon J: Pleomorphic adenocarcinoma of the pancreas. Am J Gastroenterol 60:379-386, Oct 1973

14. Kay S, Harrison JM: Unusual pleomorphic carcinoma of the pancreas featuring production of osteoid. Cancer 23:1158-1162, May 1969

15. Sommers SC, Meissner WA: Unusual carcinomas of the pancreas. Arch Pathol 58:101-111, Aug 1954

16. Shamblin WR, Priestley JT, Sprague RG, et al: Total pancreatectomy for pleomorphic carcinoma: A five-year cure. Arch Surg 92:315-317, Feb 1966

17. Tschang TP, Garza-Garza R, Kissare JM: Pleomorphic carcinoma of the pancreas—An analysis of 15 cases. Cancer 39: 2114-2126, May 1977

18. Alguacil-Garcia A, Weiland LH: The histologic spectrum, prognosis and histogenesis of the sarcomatoid carcinoma of the pancreas. Cancer 39:1181-1189, Mar 1977

19. Cubilla AL, Fitzgerald PJ: Classification of pancreatic cancer (nonendocrine). Mayo Clin Proc 54:449-458, Jul 1979

20. Hartz PH, van der Sar A: Cancerous cyst of the tail of the pancreas simulating carcinosarcoma. Am J Clin Pathol 16:219-224, Feb 1946

21. Rosai J: Carcinoma of pancreas simulating giant cell tumor of bone—Electron microscopic evidence of its acinar cell origin. Cancer 22:333-344, Aug 1968

22. Grosfeld JL, Clatworthy HW, Hamoudi AB: Pancreatic malignancy in children. Arch Surg 101:370-375, Sep 1970

23. Freeny PC, Weinstein CJ, Taft DA, et al: Cystic neoplasms of the pancreas: New angiographic and ultrasonographic findings. Am J Roentgenol 131:795-802, Nov 1978

24. Zintel HA, Enterline HT, Rhoads JE: Benign cystadenoma of the pancreas: Report of 4 treated cases, 1 by Whipple type of resection. Surgery 35:612-620, Apr 1954

25. Pyrah LN, Cowie JW: Two unusual aortograms. J Fac Radiol 8:416-420, Jun 1957

26. Carroll B, Sample WF: Pancreatic cystadenocarcinoma: CT body scan and gray scale ultrasound appearance. Am J Roentgenol 131:339-341, Aug 1978

27. Levin DC, Eisenberg H, Wilson R: Arteriography in the evaluation of pancreatic pseudocysts. Am J Roentgenol 129:243-248, Aug 1977

28. deSantos LA, Bernardino ME, Paulus DD, Marin RE: Computed tomography of cystadenoma of the pancreas. J Comp Assist Tomogr 2:222-225, Apr 1978

29. Frey CF: Pancreatic pseudocyst—Operative strategy. Ann Surg 188:652-662, Nov 1978

30. Piper CE Jr, ReMine WH, Priestly JT: Pancreatic cystadenomata: Report of 20 cases. JAMA 108:648-652, May 1962

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Hyperbaric Oxygen for Carbon Monoxide Poisoning

TO THE EDITOR: The fine article in the November 1981 issue by Dennis Landers, MD, PHD, on carbon monoxide poisoning[1] deserves some comment. In the article he shows that emission control systems on automobile exhausts have decreased the possibility of death by carbon monoxide poisoning during suicide attempts—an unexpected environmental bonus, indeed.

Although the thrust of the article is not toward treatment, he does mention oxygen therapy and neglects the most impressive modality—hyperbaric oxygen. He implies that the only treatment available is high flow oxygen to hasten the dissociation of carboxyhemoglobin. Hyperbaric oxygen will do this more rapidly, will increase the flow of oxygen to the hypoxic tissues and will decrease the cerebral edema that can cause central nervous system sequelae.[2]

This is being written to remind physicians that there are many facilities available for hyperbaric oxygen therapy. Many are related to scuba diving, some are associated with hospital therapeutic and research units. The location of the closest hyperbaric chamber can be obtained by calling the Diving Accident Network which is associated with Duke University Medical Center. The number is manned 24 hours a day. It is (919) 684-8111. In an emergency, collect calls will be accepted. Forgetting hyperbaric oxygen therapy can lead to needless morbidity and mortality.

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REFERENCES

1. Landers D: Unsuccessful suicide by carbon monoxide: A secondary benefit of emissions control. West J Med 1981 Nov; 135:360-363
2. Anderson GK: Treatment of carbon monoxide poisoning with hyperbaric oxygen. Milit Med 1978 Aug; 143:8

* * *

TO THE EDITOR: We enjoyed reading the interesting case of carbon monoxide poisoning recently reported by Landers[1]; however, his comment that carbon monoxide has "little in the way of a true toxic effect" is not quite accurate. Actually, carbon monoxide (CO) poisoning is a complex phenomenon that involves both direct and indirect toxic effects.

As noted by Landers, CO causes tissue hypoxia by disturbing blood oxygen transport. This indirect toxic effect results from the preferential affinity of CO for hemoglobin and the associated leftward shift of the oxy-hemoglobin dissociation curve. These effects are thoroughly discussed in standard references.

Less well recognized is the fact that CO also is directly toxic to the cellular cytochrome system,[2-6] with inhibition of cytochrome A_3 oxidase being the most important effect. Although there is little information available about the exact mechanism and pharmacokinetics of CO-cytochrome binding, it is believed that these direct toxic effects on cellular respiration account for the often noted disparity between carboxyhemoglobin (COHb) levels and a patient's clinical condition.

Illustrative of the direct toxicity of carbon monoxide are the six patients recently reported by Myers and co-workers,[7] in whom the COHb levels were minimal or zero but who were still profoundly symptomatic from CO poisoning. All of these patients failed to respond to standard therapy but promptly recovered following treatment with hyperbaric oxygen (HBO). We have had some similar experience.

The usefulness of and rationale for treating CO poisoning with HBO have been discussed elsewhere.[5,8-11] Among the beneficial effects are a greatly diminished carboxyhemoglobin half-life, enhanced tissue clearance of residual CO, reduced cerebral edema and reversal of the cytochrome oxidase inhibition. The specific mechanism by which HBO overcomes the cytochrome toxicity in both CO and cyanide poisoning has not been well delineated.

At present it is recommended that anyone who is symptomatic and has a COHb level of 25 percent or greater should be treated with HBO.[5] However, the history of exposure and the overall clinical appearance of the patient should be the prime determinants of who is referred for HBO regardless of the actual COHb level.

It is important that emergency physicians and other personnel involved in the care of these types of cases establish liaison with the HBO treatment facilities in their communities so that referral to such facilities can be expeditiously accomplished when needed. Contrary to what Coleman noted in her recent excellent review of smoke inhalation[12] —that is, that HBO is "seldom available in time to be beneficial" in cases of CO poisoning—HBO treatment is now readily available in many metropolitan areas. (For example, there are five hospitals in the San Francisco Bay Area which currently have one or more monoplace recompression chambers and additional facilities are expected to become available soon.) Also, as noted by Myers,[7] severely poisoned patients may have dramatic recoveries even when HBO treatment is delayed many hours. The importance of knowing the availability of HBO treatment has been further underscored by recent litigation in which large settlements were awarded to plaintiffs because they were not referred for HBO treatment when facilities for such were locally available.

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REFERENCES

1. Landers D: Unsuccessful suicide by carbon monoxide: A secondary benefit of emission control. West J Med 1981 Nov; 135:360-363
2. Goldbaum LR, Orellano T, Degal E: Mechanism of the toxic action of carbon monoxide. Ann Clin Lab Sci 1976; 6:372-376
3. Chance B, Erecinska M, Wagner M: Mitochondrial responses to carbon monoxide toxicity. Ann NY Acad Sci 1970; 174:193-204
4. Goldbaum LR, Ramirez RG, Absalon KB: What is the mechanism of carbon monoxide toxicity? Aviat Space Environ Med 1975; 46:1289-1291
5. Kindwall EP: Carbon monoxide poisoning and cyanide poisoning. HBO Rev 1980; 1:115-122
6. Somogyi E, Balogh I, Rubanyi G, et al: New findings concerning the pathogenesis of acute carbon monoxide (CO) poisoning. Am J Forensic Med Path 1981; 2:31-39
7. Myers RAM, Snyder SK, Linberg S, et al: Value of hyperbaric oxygen in suspected carbon monoxide poisoning. JAMA 1981; 246:2478-2480
8. Smith G, Sharp GR: Treatment of carbon monoxide poisoning with oxygen under pressure. Lancet 1960 Oct 22; 2:905-906
9. Sluijter ME: The Treatment of Carbon Monoxide Poisoning by Administration of Oxygen at High Pressure. Springfield, IL, Charles C Thomas, 1963
10. Kindwall EP: Carbon monoxide and cyanide poisoning, *In* Davis JC, Hunt TK (Eds): Hyperbaric Oxygen Therapy. Bethesda, MD, Undersea Medical Society, Inc, 1977, pp 177-190
11. Myers RAM, Linberg SE, Crowley RA: Carbon monoxide poisoning: The injury and its treatment. JACEP 1979; 8:479-484
12. Coleman DL: Smoke inhalation—Medical Staff Conference, University of California, San Francisco. West J Med 1981 Oct; 135:300-309

Impaired Cognitive Judgment in Relation to the Chronic Use of Anticoagulants

TO THE EDITOR: Last year, a corporation president asked about a possible relationship between anticoagulants and impaired judgment. He had noted that, in several instances, otherwise very competent and experienced senior executives had made surprisingly poor decisions or had exercised remarkably bad judgment. (Even the executives themselves, all men, were appalled and confused by their actions.) Subsequently, it had been discovered that, in every case, the individual executive was taking prescribed anticoagulant medication at the time of judgmental errors.

Cursory inquiry of area physicians suggested no such relationship or knowledge of the correlation. Several other major corporation leaders were contacted and asked to view this issue retrospectively. They were asked to determine what significant examples of poor judgment, if any, had occurred in their companies in the recent years. Nine such incidents were identified and, in reviewing the medical histories of the individuals responsible, six were shown to have been taking anticoagulant medications at the time of the inappropriate actions.

Concurrently, I discovered three of my clients who were experiencing frequent bouts of impotency were using only one medication: sodium warfarin (Coumadin, Panwarfin). In addition, two Air Force officers and five businessmen who were either then taking this same drug or had used it in the past made statements such as, "I felt strangely vulnerable and mentally uncertain," and, "It was like not having both oars in the water." Another said, "Being 63, I wondered if I was already getting senile. I couldn't remember whether I'd actually talked to someone or just thought about it." All expressed concern over resulting sexual dysfunctions. Two indicated more of a reduced libidinal drive as the cause of their unexpected lack of sexual activity rather than the inability to properly function. They reported masturbation not to be a problem while the others claimed they had not attempted it since the onset of the difficulties. (This therapist has never encountered an impotency case before or since these cases in which masturbation had not been explored by the client.) None had ever been tested by a nocturnal tumescence device (NTD) nor had any consulted a urologist, neurologist or therapist.

Another patient, a 64-year-old medical doctor, was already falling into disfavor with colleagues due to occasional surgical errors or poor work before a stroke forced his retirement. These errors reportedly occurred during operations when he needed to react quickly and accurately. In several cases, other surgeons actually had to do postoperative repair work. This had been unheard of

during his first 30 years of practice. A review of his medical history shows that after he underwent his own aortic valve operation he began taking substantial amounts of sodium warfarin. His surgical errors occurred after he was treated with the anticoagulant. He also noted a decreased frequency in sexual activity as well, which may or may not be related to the anticoagulant.

Similarly, a very bright and successful 30-year-old women, a bank officer, who was first seen due to marital problems, began suffering from phlebitis and was immediately started on a regimen of sodium warfarin by her internist. She was strongly encouraged to begin an exercise program which she did not do. She was not taking any other medication, although she had recently ended a five-year period of taking birth control pills. Within three months, she became quite alarmed by what she described as "making dumb mistakes" at work. The mistakes resulted from "snap" or "shooting-from-the-hip" type of decisions. Indeed, she had found that if she thoroughly evaluated the criteria and consequences involved, she could avoid these errors in decision making. She claimed no difference in the frequency of love-making, however.

Literature Review

One study contends that "physicians have, for a long time, failed to note that a patient who is using anticoagulant medication daily has, in effect, been converted to a hemophilia-equivalent state. This change in status requires serious psychosocial adjustment to the chronic use of anticoagulants."[1] Another cautions that if this adjustment be poor, the patient may become restless and moody. Further, he may develop an attitude towards life that is negative and generally, dissatisfied.[2] Indeed, the patient may plunge into a pronounced depression with his functioning at only a fraction of his presickness level. His employability, adaptability to normal community stresses and family life may undergo changes that are profound.

Those of us working in rehabilitative psychology and physiatry are aware of the role body image plays in one's self-esteem, security and recovery. This was also noted by Roberts.[3] The extraordinary shockwave born of a sudden shift to a status of physical vulnerability often shatters one's self-assurance. We submit that this is clearly operating in cases involving hemophilia-equivalent patients, particularly if they are also plagued by previous and imminent errors in judgment. This dual reduction in body image and self-confidence could well be exacerbated if the "machismo mystique" were operating, particularly if the person also knew that (1) small capillaries of the brain could break at the slightest bump, causing hemorrhage and internal bleeding, and (2) reduction of cognitive abilities could also be a result.

Everyday life requires degrees of risk taking that, as shown by Alby,[4] may cause "necessary risk" to suddenly change in meaning. Overprotectiveness due to hemophilia causes one to become passive instead of assertive (also see the discussion of adjustment problems within the family sphere posited by Salk, Hilgartner and Granich[5] in families of hemophiliac children). However, it must be noted here that, unlike our patients, the hemophiliac person during childhood and adolescence has the time to receive special preparation for his adult professional life.[6]

A physician handling a case requiring the use of anticoagulants is in a double bind. Whether he selects sodium warfarin (long-term and oral) or heparin (short-term and intravenous), he faces the dilemma that "too little" does no good and "too much" produces bleeding.

Hence, the hemophilia-like state often induced by the chronic use of anticoagulants requires the collaborative effort of management of the many aspects of hemophilia afforded by a team effort of various specialties. This was first insisted upon by Hirschman and Ely (1972)[7] and strongly concurred with by Griffith and Hero (1979).[2] Here, too, it is most certainly advocated.

Critically important is the intelligent and rational sharing of this information with the patient, his family, colleagues and employers. This is not deleterious or unfair to any of those mentioned. Indeed, those patients counseled expressed immense relief that they were not "going crazy" and were "feeling out of phase" for good reason. Those families and employers so advised expressed understanding in place of confusion and irritation, particularly when shown that discontinued use of the anticoagulant, due to exercise and diet control, apparently not only returns the patient to normal, but also that replacing "snap" decisions with a well-thought-out approach usually precludes much of the problem.

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REFERENCES

1. Bruhn JG, Hampton JW, Chandler BC: Clinical marginality and psychological adjustment in hemophilia. J Psychosom Res 1971 Jun; 15:207-213

2. Griffith EE, Hero N 3rd: Chronic use of anticoagulants—Psychosocial adaptation. NY State J Med 1979 Jan; 79:90-92
3. Roberts SL: Behavioral Concepts and the Critically Ill Patient. Englewood Cliffs, NJ, Prentice-Hall, Inc, 1976, p 75
4. Alby N: Aspects psychologiques de l'hemophilie. Bibl Haemat 1970; 34:83-88
5. Salk L, Hilgartner M, Granich B: The psycho-social impact of hemophilia on the patient and his family. Soc Sci Med 1972 Aug; 6:491-505
6. Izarn P: L'orientation, la formation et la vie professionnelle de l'hemophile. Bibl Haemat 1966; 26:192-201
7. Hirschman RJ, Ely LE: Personal burden in hemophilia (Editorial Notes). Ann Intern Med 1972; 651-652

The Rights of Adult Adoptees

TO THE EDITOR: I am both a medical student and an adoptee who just last July met my biological family. Naturally I was very interested in both the July article "Adoption: Pediatric, Legislative and Social Issues"[1] and the response by Xavier Gonzalez, MD, published in October.[2] I wish to respond briefly both to the article and in particular to an issue raised by Dr. Gonzalez.

I wish first to commend Drs. Davis and Brown for a very informative *and* enlightened article. There is almost no facet of adoption that is not today either a focus of controversy or in a state of flux. Primary care physicians, by the very nature of their profession, cannot help but be affected by current adoption trends.

I especially appreciated the statements by Drs. Davis and Brown concerning the adoptee's search for his (or her) biological family. I completely agree that such searching is "a quest for information . . . [and] not an attempt to find new parents."[1] My own adoptive family upbringing was very traumatic—with a divorce, child custody battle, my adoptive mother's and sister's deaths, and much bitterness. I lacked a sense of security and well-being for most of my childhood and bore emotional scars for many years. Yet *despite* all these problems, I never once entertained the thought in my search that I would be "coming home"—so to speak—to my *real* family. I was looking for biological identity and medical information, and nothing more. My family, for better or worse, is the one that raised me, and this is the view shared by all the adoptees I have met. Emotionally it simply cannot be any other way.

I wish finally to address an issue raised by Dr. Gonzalez in his letter to the editor: the natural parents' right to anonymity. My question is this: Who really has the right—for whatever reason—to permanently deny a human being his biological identity? I doubt that advocates for absolute anonymity realize that until very recently adoption proceedings commonly did not transmit even minimal medical history information to the adoptive family. In my own case, I discovered that my grandmother has systemic lupus erythematosus and that there is a general family history of respiratory diseases. I was glad to become aware of both facts. I have also spoken with another adoptee who stopped bearing children prematurely because she could no longer withstand the uncertainty of possible genetic problems. If for no other reason, certainly the need for medical information (good or bad) is sufficient and overriding justification for direct contact with biological parents by an adult adoptee.

I personally believe that natural parents have a right to general anonymity. I do not concur, however, that they have a similar right on the basis of anonymity to permanently deny knowledge of family background, medical history and siblings to an *adult* adoptee. Once direct contact has been made, the biological parents have the right to reject a relationship (and vice versa); but to deny them the basis for that first contact, appealing to the right of anonymity, seems to me to deny the more basic right of any human being—that of knowing where one originally came from.

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REFERENCES
1. Davis JH, Brown DW: Adoption: Pediatric, legislative and social issues. West J Med 1981 Jul; 135:72-77
2. Gonzalez X: Adoption and the rights of biological parents (Correspondence). West J Med 1981 Oct; 135:337

More on Neurosyphilis

TO THE EDITOR: Dr. John R. Hotson's review of modern neurosyphilis[1] in the September issue was a well-organized survey of this disease. However, Dr. Hotson's criteria for diagnosing neurosyphilis cannot go unchallenged because they reflect a logical flaw in contemporary attempts to analyze the clinical profile of this illness.

It is generally accepted that a patient with a reactive serum FTA-ABS (fluorescent treponemal antibody absorption) test has had syphilis at some time. The question is, when neurologic dysfunction develops in this patient, is he a victim of neurosyphilis or of a concurrent, unrelated neurologic disease? At present we have no adequate way of distinguishing between a "modified neurosyphilitic syndrome" and a nonsyphilitic neurological illness occurring in a person with cured or latent syphilis. The investigative technique used by Dr. Hotson and others[2] of retrospectively selecting

patients with new neurologic complaints and reactive serum FTA-ABS tests is an inexact and possibly erroneous approach, leading to the inclusion of patients who once had syphilis but now have nonsyphilitic symptoms.

Unless a patient has a positive (CSF) cerebrospinal fluid-VDRL or undergoes clear clinical resolution following treatment with a decline in the VDRL titer, it is difficult to make a definite diagnosis of neurosyphilis. We applied these criteria to our case of isolated oculomotor paralysis.[3] However, as Dr. Hotson notes, the CSF-VDRL may be negative in up to 60 percent of patients and is not a reliable screening test. Other available "diagnostic" tests for neurosyphilis also have strict limitations. The CSF-FTA is a controversial procedure and its interpretation remains in doubt, making it an unsuitable test for neurosyphilis. CSF pleocytosis may be present in a variety of central nervous system disorders, such as cerebral infarction, vasculitis and multiple sclerosis. It is, therefore, of little use in diagnosing neurosyphilis, although it may be helpful in following the response to treatment. Support for a diagnosis of neurosyphilis can be gained when there is an elevation of the CSF gamma globulin above 13 percent of the total CSF protein. This occurs in 70 percent of cases. The presence of oligoclonal bands on agarose gel electrophoresis of the CSF is also helpful. But these findings do not exclude multiple sclerosis, vasculitis and chronic nonsyphilitic infections. Penicillin-induced reversal of signs and symptoms is a helpful diagnostic observation, but care must be taken not to attribute spontaneous improvement or stabilization (which often occurs in neurologic disease) to coincidental antibiotic administration. CSF pleocytosis within three weeks of penicillin treatment was used by Hooshmand and co-workers[2] and recommended by Dr. Hotson as supporting the diagnosis of neurosyphilis. Given the variability of lymphocyte counts from lumbar spinal fluid and the likelihood of spontaneous change in any meningeal process, I suggest caution in interpreting this particular guideline. Nor is the clinician's failure to identify an alternate diagnosis sufficient grounds for a diagnosis of neurosyphilis "by exclusion." In summary, no single or combined clinical or laboratory method(s) can establish with certainty the diagnosis of active neurosyphilis in most of the "modified" cases reported. In many of these reports, the diagnosis has been made by inference, based upon a serum FTA-ABS test and new neurologic signs. Hard data have been insufficient or lacking.

If, as Dr. Hotson suggests, high doses of intravenously administered penicillin is the treatment of choice for neurosyphilis, admitting the patient to hospital will be required, increasing the cost of therapy to the patient and to the medical establishment, as well as causing the patient loss of valuable time from work and family. With these issues at stake, accurate diagnosis becomes even more imperative.

In our laboratory we are exploring the use of the rabbit infectivity test to diagnose neurosyphilis. This is an unambiguous, highly specific technique for recovering pathogenic *Treponema pallidum* from body tissue. Using spinal fluid from patients with suspected neurosyphilis, we have resurrected this method from the preantibiotic era and modified it to make it highly sensitive and clinically applicable.[4] Time will tell if this approach will help us break through the circular reasoning that has so far impeded analysis of the serological and clinical profile of modern neurosyphilis.

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REFERENCES

1. Hotson J: Modern neurosyphilis: A partially treated chronic meningitis (Medical Progress). West J Med 1981 Sep; 135:191-200
2. Hooshmand H, Escobar MR, Kopf SW: Neurosyphilis: A study of 241 patients. JAMA 1972; 219:726
3. Jordan K, Marino J, Demast M: Bilateral oculomotor paralysis due to neurosyphilis. Ann Neurol 1978; 3:90-93
4. Jordan K, Daviau J: Rabbit infectivity test in recovering *Treponema pallidum* from human spinal fluids: A potential approach to the diagnosis of neurosyphilis. Presented 18th Annual Meeting Fed of West Soc of Neurol Sci, February, 1981

The First Devil of Nutrition Cultism

TO THE EDITOR: We appreciate the journal's publication of Dr. Victor Herbert's good article on nutritional cultism.[1] Especially interesting was his labeling Satan as the first nutritional cultist; this helps connect religion and medicine at their roots. Since Indian philosophy says God and time are the same, long-term scientific observations may be more sacred than we suspect.

Indeed, God (time) has been thought to speak to man in three ways: (1) *scripture,* (2) *nature,* (3) the *divine imprint* on man.[2] Let us use these tools to see if we can tentatively identify "the apple" Eve ate and then gave Adam.

First, *scripture* (cultural fossils from early man's observation of nature) says this apple was so important that it caused man's fall from health to illness.[3] Second, scripture gives statements that may

allow us to pin down the apple's identity: (1) Before its use, man ate from garden trees (woody plants)[4]; afterward he ate from field herbs (nonwoody plants).[5] (2) Before its use earth was fertile; afterward it was not ("cursed is the ground because of you").[6] (3) After its use women had trouble raising children ("in sorrow thou shalt bring forth children").[7] (4) And although man was clearly warned away from this "tree" its fruit was pleasant and enticing.[8]

Next, let us use science to examine *nature:* (1) Field plants (grains, tubers) are starchy, and because starch is not bioavailable to humans without cooking (personal communication: July 11, 1977, John Yudkin, MB), by the time they were eating field herbs people must have been using thermal heat to prepare food. (2) When experimental animals were fed a cooked diet compared with an uncooked one of the same composition their manure decreased in fertility about 80 percent.[9] As humans have adopted the practice of letting land lie fallow at intervals or moving when land wore out, we may assume that manure from humans eating cooked food is not optimally fertile.[10] (3) Offspring born to experimental animals eating cooked food were sickly, hard to raise and often died compared with healthy offspring born to those eating the same diet uncooked.[9]

Finally, the *divine imprint* on man (innate-behavior-releasing mechanisms) shows that *visiting a burn ward or shouting "fire!" in a crowded theater* elicits negative human responses. And though humans are thus warned away from fire, we find food prepared with "burning" (thermal) fire, as contrasted with "living" (ambient and metabolic) fire, smells and tastes good.

Therefore, we may tentatively conclude that the apple that "the first demagogue of nutrition cultism," Satan, induced the first men and women to eat is cooked food. If so, we are almost all nutritional cultists by time's standard, as we continue to eat this tree's (wood fire's) apple. And since humans are still following the original demagogue of nutrition cultism, should we not be patient towards those who espouse nutritional ideas with which we disagree? Sometimes we may find a useful idea among the dross—for example, Dr. Withering and digitalis.

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REFERENCES

1. Herbert V: Nutrition cultism (Informed Opinion). West J Med 1981 Sep; 135:252-256
2. DeGrazia M: The secularization of language in the 17th century. J Hist Ideas 1980; 41:319-329
3. Malan SC (Translation): The Forgotten Books of Eden: The First Book of Adam and Eve. Cleveland, World Publishing Co., 1963, Vol 6, pp 9-10
4. Genesis 3:2 (RSV, 1953)
5. Genesis 3:18 (KJV)
6. Genesis 3:17 (RSV, 1953)
7. Genesis 3:16 (KJV)
8. Genesis 3:6 (RSV, 1953)
9. Pottenger FM: The effect of heat-processed foods. Am J Ortho Oral Surg 1946; 32:467-485
10. Douglas JM: Is "how vitamin C really works" medicine's best discovery? Nutr Today 1980; 15:30-33

Pancreatic Exocrine Function Testing

TO THE EDITOR: In his article "Pancreatic Exocrine Function Testing" in the November issue,[1] Goff concludes that serum enzyme levels are not of great value as a means of diagnosing pancreatic exocrine insufficiency. While I would agree with this conclusion, I would differ with the reason cited with respect to isoamylase analysis. Goff states that the lack of clinical usefulness of this measurement is "the difficulty in distinguishing pancreatic from salivary amylase." On the contrary, this distinction can readily be made by several well-established technical methods.[2] The deficiency attaching to assay of pancreatic-type (P-type) isoamylase as an index of pancreatic insufficiency lies rather in the fact that abnormally low values for P-type isoamylase in the serum and urine of patients with pancreatic exocrine insufficiency confirmed by the secretin test occur infrequently.[3]

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REFERENCES

1. Goff JS: Pancreatic exocrine function testing (Medical Progress). West J Med 1981 Nov; 135:368-374
2. Berk JE, Fridhandler L, Montgomery KA: Isoamylase analysis: Methods and clinical application, *In* Berk JE (Ed): Developments in Digestive Diseases, Vol. I. Philadelphia, Lea & Febiger, 1977, pp 133-152
3. Berk JE, Ayulo JA, Fridhandler L: Value of pancreatic-type isoamylase assay as an index of pancreatic insufficiency. Am J Dig Dis 1979; 24:6-10

Altitude Exposure in Sickle Cell Disease

TO THE EDITOR: In regard to the article "Risk of Altitude Exposure in Sickle Cell Disease" by Claster, Bodwin and Embury in the November issue,[1] it is interesting to see that a restrospective study finds that there is an increased incidence of vaso-occlusive crisis during exposure to altitude above 4,000 feet in patients with sickle cell disease. It is, of course, not surprising that the incidence of such painful episodes was greater for those who spent their time visiting the mountains than for

those who spent a relatively shorter time in airplane flights. I do, however, have grave doubts as to the accuracy of the investigation which was carried out in a retrospective fashion by asking the patient to recall episodes that occurred during visits and airplane travel. The fact that it was not required that the crisis be documented by visits to a physician or medical facility does cast considerable doubt on the validity of the method. In particular, it would have been interesting to have had a comparison question asking for the number of episodes that have occurred in visiting another part of the country which was at sea level, such as Los Angeles or Monterey. A critical review of the article also causes doubt as to what is meant by average risk percent in Table 2, I find this figure totally indecipherable. The authors also ignore findings that do not fit in with their general philosophy such as that vaso-occlusive crisis appeared to be more frequent in the homozygous sickle cell hemoglobin patients during their visits to an altitude of 4,000 feet than to an altitude of 6,000 feet.

My real concern with this article is with the confidently stated conclusion, which is also repeated in the abstract, that patients with sickle cell disease who have intact spleens should take supplemental oxygen during air travel. I also have difficulty in accepting the other conclusion that patients with sickle cell disease who have had no previous mountain exposure should be advised to avoid the mountains. While this advice may indeed be proved later to be based on fact, I do not think the evidence presented in this article supports the conclusion.

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REFERENCE

1. Claster S, Bodwin MJ, Embury SH: Risk of altitude exposure in sickle cell disease. West J Med 1981 Nov; 135:364-367

A Risk of Waterskiing for Women

TO THE EDITOR: In August 1981 a 36-year-old woman arrived at Seneca District Hospital in Chester, Plumas County, California. Her husband had brought her in the family car from nearby Lake Almanor. She had been water-skiing and (about one hour before arrival at the hospital) had fallen backwards into the water. She experienced a pressure feeling "like a high speed enema" and noted vaginal bleeding, "several cupfuls." Her husband became concerned and brought her to the hospital. The accident had occurred after the boat that was towing her slowed down, almost stalled and then speeded up. As the boat's speed increased, she had lost her balance and fallen backwards.

On examination in the emergency room, blood pressure was 110/60 mm of mercury, pulse 100, hemoglobin 12.7 grams per dl, hematocrit 35 percent and leukocyte count 10,600. Her blood type was A negative. Vaginal examination showed a zigzag vaginal laceration 13 cm long, extending from a point posterior to the cervix to the left vault of the vagina, high up in the vagina. During the examination, 250 ml of blood gushed out of the wound. Her blood pressure dropped to 90/50 mm of mercury. An infusion of Ringer's lactate was given.

The patient was taken to the operating room and, under general anesthesia, the laceration was closed with two layers of locked 0 chromic catgut sutures. Two small arteries in the submucous tissues bled profusely until sutured. Blood loss in the operating room was 500 ml. The patient was given two units of plasma protein fraction (Plasmonate), a vaginal pack was placed and a Foley catheter inserted.

On the next morning hemoglobin was 8.1 grams per dl and hematocrit 22.1 percent. Two units of compatible blood (packed red blood cells) were given. That afternoon, hemoglobin rose to 10.5 grams per dl and hematocrit to 30 percent. The vaginal pack and Foley catheter were removed.

On the third day she was discharged and returned to her home in central California. She received a prescription for ferrous sulfate tablets. Fifteen days later I phoned the patient to obtain follow-up information. She had some vaginal bleeding a week after the accident. Her physician cauterized the superior part of the laceration, where fresh bleeding had occurred. She stated that a hemoglobin test, done 13 days after the accident, showed 12.5 grams.

This case illustrates the importance and seriousness of the occasional vaginal (and in other cases, rectal) lacerations that can occur from waterskiing accidents in which the skier falls backwards into the water.

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Refer to: Geyman JP, Phillips TJ: A university department of family medicine after ten years (Medical Education). West J Med 136:170-178, Feb 1982

A University Department of Family Medicine After Ten Years

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The Department of Family Medicine at the University of Washington was started ten years ago after a major curriculum change in the medical school placed new emphasis on education and training of family physicians for the surrounding region in Washington, Alaska, Montana and Idaho (WAMI). This department has organized active programs in patient care, teaching and research at the university base and in a number of affiliated community sites throughout the region. The department is well accepted within the mission of the medical school. Almost a third of graduating medical students choose postgraduate training in family practice. Almost 90 percent of the graduates of the ten programs within the department's network of family practice residencies are established in active family practices, with more than two thirds settling in the WAMI region. Follow-up studies show that these graduates feel well prepared for their practices; are providing a broad range of services in rural, suburban and urban settings; are typically involved in partnership or group practice; and are generally well satisfied with their personal and professional lives.

BEFORE THE RECOGNITION of family practice as the 20th specialty in US medicine in 1969, family practice had no formal place in medical education and lacked an organized base in most medical schools. The first decade of the specialty's development has recently been completed and the situation today is quite different. There are academic departments of family practice in 94 of the 130 medical schools in the country and family practice divisions or programs in another 20 medical schools. It is now possible to assess and characterize the roles of established departments in patient care, teaching and research.

Some fundamental questions were inevitably encountered and addressed by the founders and developers of departments of family practice in medical schools: What kind of role should this new department have in patient care? Should it be based in the academic medical center itself or in a community setting? What role should the department play in undergraduate medical education? How can family practice gain access to an already full and highly structured curriculum? How should graduate training in family practice be organized? Will such residency training meet

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ABBREVIATIONS USED IN TEXT

CME = continuing medical education
WAMI = Washington, Alaska, Montana and Idaho

the future practice needs of graduates? Can student interest in family practice be developed and sustained? Can sufficient numbers of qualified faculty be recruited, and what mixture of background and skills is needed? How can a university-based department of family practice develop and maintain ties with the community served? What kinds of linkages are desirable with other university resources? What kinds of research are needed in family practice, and how can an active research program be organized? Will the graduates of the department's residency programs locate in areas of need? Will they be challenged by and satisfied with their practices? Can the new department of family practice gain acceptance in the competitive and sometimes hostile environment of an academic medical center traditionally more oriented to tertiary care and research than to primary care?

Each academic department of family practice has addressed these questions and developed its own structure and activities within the constraints of available resources, institutional needs and support, and local patterns of patient care and teaching. Although there is considerable diversity among departments of family practice in US medical schools, the objectives and roles of these departments are quite similar. The literature to date is devoid of a published account of the profile and experience of an established academic department of family practice in this country. This paper will therefore describe the ten-year experience of the Department of Family Medicine at the University of Washington School of Medicine. The purpose of this paper is threefold: (1) to summarize the overall development of the department by describing its activities in patient care, teaching and research, (2) to present some benchmarks of the effectiveness of departmental programs and (3) to outline some of the lessons that have been learned from this experience.

Evolution of the Department

An Overview

The Department of Family Medicine of the University of Washington had its inception in the medical school's curriculum change of 1968, which placed major emphasis on education and training of family physicians for the state of Washington and the surrounding region. Subsequently, in the summer of 1970, it became a division of the Dean's Office (Division of Family Medicine) and in February 1971 departmental status was conferred. At that time it was approximately the tenth such department in a United States medical school.

With the advent of a new curriculum in 1968 at the University of Washington School of Medicine, four curricular pathways were created for students: family physician, clinical specialist, behavioral scientist and medical scientist. Over the years, the family physician and clinical specialist pathways have attracted a majority of students from each medical school class. The behavioral scientist pathway was discontinued in 1978 due to limited student interest. The medical scientist pathway has attracted a small number of students pursuing concurrent MD-PHD degrees.

As the only medical school for the four-state region of Washington, Alaska, Montana and Idaho (WAMI), the University of Washington became heavily involved in decentralized regional medical education with the development of the WAMI program in 1970.[1] Gradually the class size was increased from 85 to 175, with a total of 50 positions in each class allocated to applicants from Alaska, Montana and Idaho. As a major part of this program, clinical clerkships were assembled for medical students throughout the WAMI region involving the departments of family medicine, internal medicine, pediatrics, obstetrics-gynecology and psychiatry. Thus, two major shifts in the medical school's mission—a new curriculum favoring flexibility and primary care options, and an expanded regional focus—provided impetus to the evolution of family medicine.

Faculty

In the earlier years of the Department of Family Medicine, faculty were recruited primarily from community practice. In recent years, as family practice residencies and faculty development fellowship programs have become established, a number of new faculty members have joined the department after completion of these kinds of training programs, and actual practice experience is now more variable. Because family medicine is a relatively low clinical income specialty compared with other more procedurally oriented departments, a solid base of institutional

TABLE 1.—*Funding Sources for University of Washington Department of Family Medicine Faculty 1980-1981, Based on Full-time Faculty Equivalent (FTE)**

Academic Rank	Funding Sources: Washington State Budget (FTE)	Alaska, Montana and Idaho (FTE)	Granting Agencies (FTE)	Total
Professor	2.0	..	..	2.0
Research Professor	..	..	.4	.4
Associate Professor	6.0	..	..	6.0
Assistant Professor	3.0	3.4	3.6	10.0
Research Assistant Professor	..	..	.5	.5
Clinical Assistant Professor	..	..	.6	.6
Clinical Instructor	..	..	.5	.5
Research Associate	..	..	1.75	1.75
TOTAL	11.0	3.4	7.35	21.75

*Includes training grants from W. K. Kellogg Foundation, Robert Wood Johnson Foundation and the Department of Health and Human Services, Public Health Service, Health Resources Administration, Bureau of Health Manpower.

support has been required to recruit and retain faculty. The current distribution of the full-time, university-based academic faculty by rank and funding source is shown in Table 1.

In order to carry out the sizable teaching commitments of the department for both medical students and residents throughout the WAMI region, a large clinical faculty has been developed. There are now more than 220 clinical faculty members in the department, most of whom are active in family practice in the community. About 20 of these are in full-time teaching in affiliated family practice residency programs through the support of their own institutions or through state funds appropriated to the university for allocation to these residency programs.

Patient Care

To provide a teaching and research base in the medical school, it was considered essential to develop and maintain an active university-based clinical service in family medicine. Accordingly, a Family Medical Center was built contiguous to the University Hospital on the ground floor with convenient patient access. This unit functions as an autonomous group teaching practice involving faculty, residents and students. Together with the family medicine inpatient service, it provides a visible family medicine presence in the medical school, thereby enhancing the exposure of medical students and other faculty to this discipline.

The Family Medical Center has 15 examination rooms, a waiting-reception area, a small office laboratory, a minor surgery room, a conference room and business offices. Medical records are maintained separately from the hospital on a problem-oriented and family basis. The focus of the practice is on continuity and comprehensiveness of care. Consultation is readily available from the other clinical departments on both an ambulatory and inpatient basis, and during the academic year 1980-1981 the consultation rate was 15 percent.

The Family Medicine Inpatient Service is nongeographic within the university hospital, having access to beds on several medical floors, labor and delivery areas and the newborn nursery. During the 1980-1981 academic year, there were 534 patients admitted to the hospital on this service, including 166 obstetric patients.

Because of various constraints including space limitations, availability of faculty and staff and extensive commitments of the faculty in teaching and research, the maximal clinical volume of the Family Medical Center is estimated at about 20,000 patient visits a year. Over the last ten years, the teaching practice has grown steadily and already exceeds 18,000 patient visits a year. The Family Medical Center now comprises about 13 percent of all outpatient visits.

An important goal in the initial planning of the department's clinical service was the development of a broad-based patient population representative of the community in terms of age, sex, ethnic and socioeconomic distribution. The department provides ongoing primary care for approximately 6,500 patients (2,500 families). The age distribution of the practice population reflects the general Seattle population, with about 28 percent of the patients younger than 18 years of age and 10 percent older than 60 years of age. About 60 percent of the patients are female, reflecting the higher rate of visits by women that is customarily seen in primary care. In terms of third-party coverage, 60 percent of the practice is covered by private insurance, 24 percent by Medicaid, and 11 percent by Medicare.

Education

Undergraduate. The Department of Family Medicine's first educational efforts were directed to the development of an undergraduate teaching program for medical students, which was launched two years before a residency program was started. Since then, a sizable undergraduate teaching program has been developed with elective offerings

TABLE 2.—*The Family Practice Residency Network, University of Washington, as of 1981-1982*

Program Sites	*Number of Residents*	*Year Started*
University Hospital, Seattle	18	1972
Doctors/Swedish Medical Center, Seattle	24	1972
Group Health Cooperative, Seattle	12	1972
Family Medicine Spokane	19	1972
Madigan Army Medical Center, Tacoma	25	1972
Providence Medical Center, Seattle	12	1974
Family Medicine Yakima*	12	1975
Southwest Idaho, Boise	18	1975
Family Medicine Tacoma	12	1978
Naval Regional Medical Center, Bremerton	10	1981
TOTAL	162	

*The Yakima program is a "one-and-two" program, with the first year in Spokane hospitals and the next two years based in Yakima.

in all four years of the medical school's curriculum. Although the required first-year course, Introduction to Clinical Medicine, is an interdisciplinary, nondepartmental course, family medicine faculty have chaired this course for seven years and play a major role in teaching. Other teaching activities during the preclinical years include an introductory family medicine preceptorship (half a day per week for one quarter of the first year) and a continuity family medicine clerkship (half a day per week for three quarters of the second year). Both of these courses are conducted jointly with clinical faculty members practicing in the community.

The family physician pathway has consistently attracted approximately half of each class over the years.[2] The two major differences between this and the clinical specialist pathway are (1) the requirement of a family medicine clerkship and (2) the active involvement of family medicine faculty role models as advisors to students in the family physician pathway.

The family medicine courses during the clinical years are decentralized to a variety of teaching sites throughout the WAMI area. The third-year six-week basic clerkship in family medicine is conducted at University Hospital and in all of the affiliated family practice residency programs. The six-week community clinical clerkship in family medicine is offered during the latter part of the third year and throughout the fourth year in one of eight group practices in the WAMI area. Six of these practices are located in small towns and rural communities—Anacortes and Omak, Washington; Ketchikan, Alaska; Kalispell and Whitefish, Montana; and Pocatello, Idaho—while the other two teaching groups are located in larger communities of Washington (Spokane) and Alaska (Anchorage). In addition, a fourth-year family medicine preceptorship of variable length is offered in several underserved National Health Service Corps and Indian Health Service sites in the WAMI region, and some elective preceptorships are also available in selected primary care settings overseas in developing countries.

Family medicine faculty have contributed regularly to other portions of the required preclinical curriculum, including courses entitled Musculoskeletal System, Behavioral Systems, Ages of Man, Epidemiology, and an elective course entitled Medicine, Health and Society. In addition, a family medicine research elective has attracted a number of students, particularly during the last several years.

As is the case with many medical schools, an intensive reassessment of the medical school's curriculum has recently taken place. Several revisions of the curriculum have been made, including termination of the pathway system, definition of a standard core of clinical clerkships for all students, development of new electives and modification of the advising system. Family medicine now has a place in the core clinical curriculum whereby medical students can obtain their required credits through several course options during the second, third, and/or fourth years.

Graduate. From the outset, it was considered important to establish residency programs in varied settings and to decentralize the locations. The family medicine residency program at University Hospital was started in July 1972. Before that, two other family medicine residencies had been started in Seattle: the Group Health and the Doctors' Hospital programs (1969 and 1970, respectively). Family Medicine Spokane, with three participating hospitals in Spokane, was also begun in 1972. These three programs were formally affiliated with the university in that year. In 1974 a fourth affiliated program in Seattle was started at Providence Hospital and in 1975 two additional affiliated family practice residencies were started in Yakima, Washington, and Boise, Idaho. Three years later an affiliated family medicine residency was started at Tacoma, Washington. More recently, affiliations have been established with two military family medicine residencies at Madigan Army Medical Center in Tacoma and at the Naval Regional Medical

Center, Bremerton, Washington. Table 2 shows the number of residents now in training in these programs, which comprise all of the operational family medicine residencies in the WAMI region.

With the acquisition of a grant from the Kellogg Foundation in 1975, together with state funds earmarked for this purpose in Washington and Idaho, a regional network has been established integrating all affiliated family medicine residency programs.[3] The major goals of this network have been as follows:

- Expansion of the network to more nearly meet the needs for both adequate numbers and distribution of family physicians in the WAMI region.
- Sharing of educational and evaluative resources among participating programs to increase the quality of resident training.
- Development of data-retrieval systems for ambulatory and inpatient resident experiences for the purposes of program evaluation, improvement of resident training and research.
- Development of the residency-based Basic Clerkship in Family Medicine for third-year medical students.
- Generation of new research and development activities in specific areas of interest.

Through regular meetings of family medicine faculty in the network, collaborative efforts have been directed to filling various common needs, such as curriculum and faculty development, program evaluation, solving operational problems and coordination of resident rotations and electives.

Continuing Medical Education (CME). The major focus of the department's activities in CME has been a one-week family practice review course, which in recent years has been offered twice each year. Some family medicine faculty have contributed to interdisciplinary CME programs in such areas as sports medicine, office orthopedics, geriatrics, behavioral science and alcoholism. Other departmental programs include the development of self-assessment techniques and self-teaching materials, individualized short-term (two to four weeks) CME programs in selected areas and studies of learning styles and educational needs of practicing family physicians.

Research

The initial priorities during the earlier years of the department's development were necessarily the organization of patient care and teaching programs for both medical students and residents, together with the establishment of interactive linkages with community-based family physicians and teaching programs throughout the WAMI region. In 1977 a research section was organized in the department with three principal functions: (1) It designs and conducts research projects based in family medicine. (2) It acts as a source of consultation and support to members of the full-time and clinical faculty and to the community at large in the area of research and scholarly investigation. (3) It administers a major fellowship training program for postgraduate family physicians through funding from the Robert Wood Johnson Foundation.

An interdisciplinary advisory group to the research section was established early, which includes representatives from the clinical departments and from departments in other schools (for example, biostatistics, epidemiology, health services, behavioral sciences and anthropology). This advisory group, together with an intradepartmental steering committee, has helped to formulate policy for both the research section and the two-year family medicine fellowship program.

Four general themes of research have emerged in the Department of Family Medicine:

- Clinical epidemiology—stressing population-based clinical strategy research and utilizing the resources of the residency network and affiliated WAMI teaching practices.
- Health services research, particularly in rural health care.
- Behavioral medicine—with an emphasis on sociocultural issues and family function.
- Clinical cognition and decision making.

A number of research projects have already been completed or are in progress in all of these areas. A major three-year grant has been received from the National Institutes of Health to support a regional study of physician and patient behavior in the control of insulin-dependent diabetes mellitus. This project involves collaboration with the Department's WAMI teaching group practices and with the University of Washington Diabetes Research Center, and represents a role that the department can effectively play in many applied population-based research projects.

Some Measures of Departmental Impact

Departmental Acceptance

After ten years the Department of Family Medicine has become fully integrated into the

School of Medicine activities in the areas of patient care, teaching and research. Departmental faculty have a substantial role in undergraduate teaching, and the family medicine residency network makes up about a quarter of all house staff positions in University of Washington affiliated hospitals. Considerable interaction and collaboration takes place regularly between the Department of Family Medicine and many other departments. Departmental faculty are active members on major committees in the School of Medicine, such as the Executive Committee, the Academic Affairs Committee, the Admissions Committee and various search committees for departmental chairmen.

Student Interest

A high level of interest in family medicine was achieved early and maintained consistently throughout the 1970's. Table 3 shows the proportion of each class between 1969 and 1980 that selected the family physician pathway. Table 4 shows the proportions of each graduating class from 1972 to 1981 that entered five major categories of internship and residency training. Family practice residencies have continued to attract 25 percent to 33 percent of the graduates, and some of those entering rotating or flexible training programs later enter family practice residencies.

TABLE 3.—*Family Physician Pathway Selection as of 1979-1980*

Year Entered	Graduation Year	Class Size	Family Physician Pathway No.	(%)
1978	1982	177	67	(38)
1977	1981	183	85	(46)
1976	1980	175	89	(51)
1975	1979	172	87	(51)
1974	1978	135	70	(52)
1973	1977	129	60	(46)
1972	1976	120	60	(50)
1971	1975	106	37	(35)
1970	1974	95	38	(40)
1969	1973	84	42	(50)
1968	1972	85	5	

Distribution of Residency Graduates

A total of 267 family physicians have now graduated from family practice residencies in the network. These graduates are distributed as shown in Table 5. About 70 percent of the graduates remain in the WAMI region, with almost 90 percent of these graduates established in family practice. Of the graduates in active practice, 46 percent are in urban communities (more than 100,000 people), 37 percent in rural and small communities (fewer than 25,000 people) and 17 percent in suburban or medium-sized communities (ranging from 25,000 to 100,000 people). Although the family medicine residency network has grown considerably during the last eight years, the annual number of residency graduates is still short of the region's needs.

Quality of Residency Training

There are several measures supporting the overall quality of residency training as provided within the network. At least 400 applications are received each year for the 54 first-year residency positions available. All of the residency programs are fully accredited. The attrition rate from the network during the last five years has been about 3 percent each year, and over 97 percent of graduates have been certified by the American Board of Family Practice. On the basis of a recent graduate follow-up study, with 93 percent responding, most graduates felt adequately prepared for medical practice.[4]

Practice Patterns of Residency Graduates

Based on a survey of 119 of the 128 network graduates through 1978,[4] the following findings are of particular interest:

- Single-specialty, fee-for-service group practice (that is, three or more family physicians) is the most common practice mode, representing 32 percent of graduates, while 10.1 percent are in partnership practice and 17.7 percent have chosen solo practice; an additional 8.4 percent of

TABLE 4.—*Choice of Internship and Residency by Percentage of Graduating Class for Years 1972 through 1981*

Type of Residency	Year of Graduation 1972	1973	1974	1975	1976	1977	1978	1979	1980	1981
Rotating/flexible	28	22	23	9	9	8	9	8	18	9
Family practice	4	28	26	31	27	31	25	28	30	33
Internal medicine	34	34	30	26	28	33	29	28	20	30
Pediatrics	14	6	4	10	6	8	6	6	6	4
Surgery/surgical specialties	10	6	10	9	18	9	8	14	15	17

graduates are in the military or in the National Health Service Corps.

- Five percent of network graduates have entered full-time teaching in either a medical school or a community hospital-based residency.
- The average workweek for full-time family physician graduates is 59.5 hours, including 51 hours in direct patient care, 3.7 hours in continuing medical education and 2.1 hours teaching students or residents.
- Network graduates report a relatively wide spectrum of practice (for example, about 90 percent include obstetrics in their practice).
- All of the network graduates maintain privileges on the active staff of one or more hospitals; of the family physicians practicing full-time, 90 percent are satisfied with their hospital privileges.
- Almost 93 percent of network graduates use problem-oriented medical records; nearly 20 percent use some kind of data-retrieval system.
- Among the graduates in full-time family practice, 41 percent have physician extenders (Medex, physician assistant or nurse practitioner).

TABLE 5.—*Location of Network Graduates as of August 1981*

Remaining in WAMI Region		187
Washington	157	
Alaska	7	
Montana	8	
Idaho	15	
Left WAMI Region		70
In private practice	42	
In military	28	
Undecided		10
TOTAL		267
In WAMI Region by activity		
Community practice		
Population less than 2,500		28
2,500-25,000		30
25,000-50,000		24
50,000-100,000		3
100,000+		72
Teaching		
Full-time teaching in family practice residency		6
UW research fellowship		3
Other		
Emergency room		8
Psychiatry		1
Locum tenens and miscellaneous primary care activities		12
TOTAL		187

- About a third of the graduates expressed definitive interest in future research studies in collaboration with the department.
- Graduates of network programs who are in full-time family practice are well satisfied with their personal and professional lives and feel well prepared for most of their practice needs.

Some Lessons From This Experience

The following points emerge as important lessons from the first ten years in the development of the Department of Family Medicine at the University of Washington:

Staged Development and Controlled Growth

It was recognized early that the new department could not address effectively all parts of its mission at once and that priorities for staged development were required. The department's initial activities in 1970 were directed to the development of various undergraduate teaching programs for medical students. In 1972 the university-based teaching practice was begun with the opening of the Family Medical Center, which made possible the start of the university-based residency program. At the same time, the first affiliations were established with three community-based residency programs. In 1975, through support of state funds and a grant from the Kellogg Foundation, a network was established joining the department with all of the community-based family practice residencies in the region. Before a major emphasis could be placed on research, it was necessary to consolidate these programs and recruit additional faculty. With that accomplished, a research section was started in 1977, followed in 1978 by a two-year family medicine fellowship program through funding provided by the Robert Wood Johnson Foundation.

Need for a Strong Faculty Core

In the earlier years of the department, a small cadre of full-time faculty was overburdened with the many demands of patient care, teaching and organization of departmental teaching programs both at the university and at a far-flung group of affiliated community settings. It became clear that additional faculty were needed to help start a research program and to allow a balanced involvement in patient care, teaching, research and administration. At its present faculty size, the department can function effectively in all of these

areas and still allow individual faculty members time for research and related scholarly work.

Value of University-based Practice

The development of a clinical practice in the Family Medical Center and in University Hospital has been a critical step in the progress made by the department in patient care, teaching and research. The university-based practice has allowed physician faculty to maintain practice skills and has provided the patient-care base for a variety of teaching and research activities. The understanding by other faculty in the medical school of the role and training of the family physician has been helped by close proximity to a visible family medicine program. In addition, the importance of family physician faculty being readily available to medical students as teachers and role models cannot be overestimated.

Importance of Complementary "Mix" of Faculty

To maintain the department's clinical base in patient care, it became evident that most of the full-time faculty had to be physicians with enough clinical breadth to attend in the Family Medical Center and on the family medicine inpatient service. Most faculty members are involved in the ongoing care of both adults and children, including obstetric practice; surgical skills are more variable among the faculty and most commonly involve ambulatory minor surgical procedures. Although most of the physician faculty maintain a common core of clinical skills, each also develops expertise in special interest areas (for example, geriatrics, sports medicine, clinical decision making, health services research). It has also been found essential to recruit some full-time nonphysician faculty in other disciplines such as behavioral science (clinical and social psychology), clinical epidemiology and medical education. In addition, some joint and adjunct appointments have been established for part-time faculty based in other departments and schools in the Health Sciences Center.

Continuity of Patient Care for Families

Over the years, some faculty and groups have held various expectations of the potential clinical roles of a family medicine program in this university medical center. For example, the department was asked on several occasions whether it would accept a major clinical and administrative role in the emergency room of University Hospital. On the one hand, this seems a logical request in view of the clinical breadth of the family physician and the integral nature of emergency medicine as one facet of the family physician's training and practice. In other respects, however, emergency medicine is the antithesis of family medicine because of its emphasis on episodic rather than comprehensiveness of care. To limit the clinical commitments of a comparatively small family medicine faculty to a reasonable level without compromising other departmental commitments in teaching and research, it has been necessary to concentrate the department's clinical commitments in the context of long-term comprehensive continuity of care of families based in the Family Medical Center.

Importance of Community Linkages

To carry out extensive and needed departmental teaching programs for both medical students and residents, it has been absolutely essential to develop close affiliations with many community-based practice groups and residency programs throughout the WAMI region. This has provided students and residents with excellent "real world" learning experiences, thereby circumventing the inevitable limitations of large academic centers in primary care teaching. In addition, decentralization of the department's teaching programs has probably played a significant role in achieving high levels of retention of network residency graduates in communities of all sizes throughout the WAMI region. The collaborative relationships that have been established between the full-time university-based faculty and family medicine faculty in community-based affiliated programs and practice have been mutually productive in many ways, including reality-testing of departmental programs, faculty development and, more recently, the initiation of some collaborative research projects.

Quality of Decentralized Teaching Programs

The experience of this department over the last ten years has demonstrated that excellent teaching programs (as measured by student, faculty and peer evaluations) can be established and maintained in decentralized settings away from the university. A number of quality control techniques have been developed to monitor student and resident experience, performance and progress, together with evaluating the overall program.[3,5,6] The cooperative climate that has been

established over the years between university- and community-based faculty should assure the future vitality of these programs.

Importance of Institutional Support

Since family medicine is inevitably a relatively low revenue-generating department in comparison with the more procedurally oriented surgical and medical specialties, a solid base of institutional support is needed for such a department to achieve its goals in patient care, teaching and research. In this instance, patient care revenue supports the operation and staffing of the Family Medical Center only. State funds provide a floor of funding support for about 60 percent of the centrally administered departmental budget, including about half of faculty salaries and the salaries of all university-based residents. Extramural grants have provided funding for the salaries of other faculty and staff. The progress that has been made by this department to date would not have been possible without the solid support of the administration and the constructive assistance of other departments in the medical school.

Sustained Student Interest in Family Medicine

There was a feeling by many observers during the late 1960's and early 1970's that family medicine might represent a flash-in-the-pan phenomenon. However, this department's experience has been that of a high level of interest sustained among medical students in this specialty that shows no signs of erosion. This is not surprising in view of the positive correlations that have been demonstrated nationally between increased numbers of students choosing family practice and such factors as the presence of a department of family medicine and full-time family physicians on the faculty.[7]

Residency Graduates Meet Expectations

The results of a recent survey of graduates from the University of Washington Family Medicine Residency Network show that these graduates are meeting public and personal expectations for these programs.[4] Retention in the field of family medicine and in the region served by the network is high, and a broad range of services is being provided by the graduates. They are evenly distributed among communities ranging from rural to urban and maintain active hospital practices. That these graduates have expressed a high level of satisfaction with their personal and professional lives, together with considerable interest in maintaining ties to the department for teaching, research or both, augurs well for the continued effectiveness of these programs.

REFERENCES

1. Schwarz MR: WAMI—An experiment in regional medical education (Medical Education). West J Med 121:333-341, Oct 1974

2. Phillips TJ, Gordon MJ, Leversee JH, et al: Family physician pathway and medical student career choice—Ten years after curriculum change at the University of Washington. JAMA 240: 1736-1741, Oct 13, 1978

3. Geyman JP, Deisher JB, Gordon MJ: A family practice residency network: Affiliated programs in the Pacific Northwest. JAMA 240:369-371, Jul 28, 1978

4. Geyman JP, Cherkin DC, Deisher JB, et al: Graduate follow-up in the University of Washington Family Practice Residency Network. J Fam Pract 11:743-752, 1980

5. Zinser EA, Wiegert HT: Describing learning experiences of undergraduate medical students in rural settings. J Fam Pract 3: 287-291, Jun 1976

6. Phillips TJ, Swanson AG, Wiegert HT: Community clinical clerkships for educating family medicine students: Process of development (a WAMI progress report). J Fam Pract 1:23-27, Nov-Dec, 1974

7. Beck JD, Stewart WL, Graham R, et al: The effect of the organization and status of family practice undergraduate programs on residency selection. J Fam Pract 4:663-669, Apr 1977

Refer to: Fox ERW: Commentary from Coeur d'Alene (Commentary). West J Med 136:179-180, Feb 1982

Commentary

Commentary from Coeur d'Alene

E. R. W. FOX, MD, *Coeur d'Alene, Idaho*

AT THE 1981 annual meeting of the Washington State Medical Association Senator Slade Gorton presented a comprehensive résumé of the various health care proposals now being considered by Congress. Each of the programs now under study is designed to promote competition or consumer choice. The buzzword is "procompetition."

It is finally being recognized that full coverage, first dollar insurance has resulted in an expanded demand for health care. Politicians are now discovering what organized medicine tried to tell them way back when the Medicare and Medicaid programs were being formulated.

Of the various plans under consideration—health care vouchers, multiple choice of insurance plans, minimum benefit standards, a cap on the nontaxable premium contributions, deductibles, coinsurance, copayments—none seem to be getting unqualified support. In fact, there is strong opposition coming from labor unions, the insurance industry, even the Gray Panthers.

At the conclusion of his talk, Senator Gorton urged doctors to work with the administration and Congress "to produce a bill that would serve the public interest and begin to solve these critical problems in the delivery of health services." The Senator should know that several medical organizations including the American Medical Association, the American Academy of Family Practice and the American Society of Internal Medicine, have long been ready to join in a cooperative effort. Being on the inside, they could have valuable advice.

Our role as individuals in this effort to "solve these critical problems" is less easy to define. Even though we physicians insist that, even now, the spirit of competition is alive and well in the practice of medicine, every one of us must admit that the present method of payment for services has its faults—faults that often weigh heavily in our favor.

Has not each of us, now and again, scratched his head in wonder at being paid for a service that in bygone days we gladly rendered for free? Although most of us pay little attention to pricing practices we will admit that on those occasions when we have had the opportunity of looking at fee schedules, some of the procedures seemed grossly overpriced.

We have soothed our consciences by saying that the higher fee for the easy services balances out the lower pay for the tougher ones. Or, we throw up our hands and say it is futile to try to fight the system.

Our colleagues in the "super specialties," who do the cardiac catheterizations, the total hip replacements, the neurosurgery, the open heart surgery, will honestly concede that there is an inequity in their fee schedule. High fees were justified when the procedures were new, the risks great, the experience limited. But now that they are becoming more commonplace, with risks diminished by vastly improved technology and experience, the price charged remains the same. The "supply side" theory has not been allowed to function. Consider the dilemma of an orthopedic surgeon in our area who, conscience-stricken, submitted a lesser fee for a hip replacement. It didn't work. The computer spat an "improper charge" back at him.

Sad to say, our hospitals are part of the problem. Thanks to the third party payors, hospitals are profit-making institutions. By being required to "itemize," they now are paid for services—

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catheterizations, enemas, surgical preps—that yesteryear were part of the package. And the day of disposables has arrived because the government and the insurors will pay for paper gowns and drapes but not for laundering services.

The American Society of Internal Medicine (ASIM) has come forward with a solution to this "economic health care crisis," so simple and straightforward that it probably won't get the congressional attention it deserves. The members of ASIM contend that government should quit paying such high fees for measurable, tangible procedures and begin to raise the fees for "cognitive" services.

This concept will be attacked as being simplistic. Yet, no one can doubt that costly hospital practices have been given preference over the services we render in our offices. X-ray studies, laboratory tests, surgical procedures, emergency room visits all enjoy far higher remuneration than the history taking, the talking, the thinking, the time-consuming evaluating that go into making a diagnosis and formulating a treatment plan.

It is anticipated that physicians who render "procedural" services will not readily accept this concept. But the ASIM insists that if their plan is fully understood there will be acceptance. The chairman of the ASIM task force said it well: "I honestly feel proceduralists ought to be paid better for their cognitive services and perhaps less for their technical work. I'm not demeaning technical work, but rather enhancing thinking. After all, procedures go out of style; thinking doesn't."

Refer to: Norman DJ, Barry JM, VanderWerf BA: Regional kidney sharing program for patients with broadly reactive lymphocytotoxic antibodies (Information). West J Med 136:181-183, Feb 1982

Information

Regional Kidney Sharing Program for Patients With Broadly Reactive Lymphocytotoxic Antibodies

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ABBREVIATIONS USED IN TEXT

IOB = (New England) Interhospital Organ Bank
OHSU = The Oregon Health Sciences University
SEOPF = Southeastern Organ Procurement Foundation
WATS = Western Association of Transplant Surgeons

SOME PATIENTS with chronic renal failure may never benefit from recent advances in cadaveric renal transplantation[1-5] because they have broadly reactive lymphocytotoxic antibodies. For such persons, finding an acceptable kidney from the pool of cadaver kidneys available to a single transplant center is often difficult. However, if a kidney donor can be found with whom the recipient with antibodies does not react in the crossmatch, graft survival is not adversely affected by the presence of non-donor-directed anti-HLA antibodies.[6]

To increase the pool of kidneys available to patients with lymphocytotoxic antibodies, the member laboratories of the Western Association of Transplant Surgeons (WATS) began a serum exchange and kidney sharing program in the fall of 1978. In this communication, we report our experience with this successful and continuing program during its first 30 months.

Methods

The member transplant centers of WATS that participate in this program are The Oregon Health Sciences University, Portland; the Phoenix Renal Transplant Center, Phoenix; the Arizona Health Sciences Center, Tucson; the University of California, Davis; the Pacific Medical Center, San Francisco; the University of California, San Diego, and the University of Utah Medical Center, Salt Lake City.

The Oregon Health Sciences University (OHSU) Transplant Program coordinates the serum exchange. Each month participating WATS member laboratories send current sera from highly sensitized (greater than 80 percent panel reactivity) patients to the OHSU histocompatibility laboratory. Single Terasaki trays containing sera from all patients are made by the laboratory and sent to participating centers. These trays contain the most recent and most reactive sera of all patients in the program, and both are used in the crossmatch. Crossmatch results are recorded directly onto accompanying work sheets which list the names and transplant centers of all patients. In the case of a negative crossmatch, it is the prerogative of the retrieving center to choose whether or not to export a kidney. A gentlemen's agreement regarding quality of kidneys ensures that kidneys that normally would not be used at the retrieving center are never exported. The average number of patients participating in the program per month during 1980 was 43.*

The four crossmatch techniques currently in use by participating laboratories are (1) the standard National Institutes of Health's, (2) extended complement incubation, (3) antiglobulin and (4) fluorochromasia. There is no single technique used by all laboratories. In 1980 unknown sera and cells were sent to participating laboratories for use in a crossmatch to determine concordance among the laboratories' results. Other

From the Renal Transplant Service, Divisions of Nephrology and Urology, The Oregon Health Sciences University, Portland, and the Phoenix Renal Transplant Center, Phoenix, Arizona.

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*Mary Beach, Alice Bush, Mary Ann Head, Paula Wetzsteon, Myrna Durr and Corliss Mukaigawa of The Oregon Health Sciences University Laboratory of Immunogenetics and Transplantation prepare the WATS trays for distribution. Also, the efforts of the participating laboratories and coordinators in obtaining and sending the individual sera to the OHSU laboratory are essential to the program's success.

TABLE 1.—*Kidney Sharing as a Result of a Negative Crossmatch on the WATS Tray*

Date of Transplant	*CAD T.T.**	*Recip. T.T.**	*PRA†*	*From‡*	*To§*	*Patient Status‖*
1. . . 11/14/78	2,12,35	2,28,12,15	80	San Francisco	Portland	Functioning at 31 months
2. . . 05/21/79	2,8	1,2,8,14	99	Portland	Davis	Patient died
3. . . 07/31/79	11,7,35	3,7,35	80	Portland	Davis	Functioning at 23 months
4. . . 12/25/79	2,25,7,8	2,7,8	99	Portland	Phoenix	Functioning at 18 months
5. . . 09/02/80	2,29,7	2,7,15	99	Phoenix	Portland	Functioning at 10 months
6. . . 11/19/80	1,32,44,51	1,2,12,18	100	San Diego	Davis	Patient died
7. . . 01/16/81	2,11,22,60	1,2,5,40	75	Phoenix	San Francisco	Rejected at 2 weeks
8. . . 04/27/81	32,33,14,35	29,12,40	100	Phoenix	Davis	Patient died

CAD T.T. = cadaver tissue type; Recip. T.T. = recipient tissue type; PRA = panel reactive antibodies

*Identified HLA-A and HLA-B antigens.
†Panel reactivity = percent of panel killed.
‡Center retrieving kidney.
§Recipient center.
‖As of July 1, 1981.

quality control measures are planned for the future.

Results

Since November 1978 there have been 17 WATS tray crossmatch negative kidneys sent to participating centers. Eight of these kidneys were transplanted into highly sensitized recipients (Table 1) and four are functioning after 10, 18, 23 and 31 months, respectively. Five additional kidneys were exported for moderately sensitized patients at remote centers which have limited access to cadaver kidneys. Three of these kidneys are functioning at 2, 3 and 4 months. Four patients had a positive crossmatch at the recipient center in spite of a negative WATS tray crossmatch at the retrieval center. These kidneys were not wasted, however, as they were transplanted into other patients at the receiving centers.

Discussion

The keys to the success of this program are the serum exchange and the gentlemen's agreement about organ quality and prerogative of the retrieving center. The serum exchange allows the center that retrieves a kidney to carry out a crossmatch on sensitized patients from other centers before exportation of the kidney. This increases the probability that the crossmatch will be negative at the recipient center. The serum exchange also gives each center in the WATS program a greater opportunity to find crossmatch negative kidneys for their sensitized patients from a much larger cadaver kidney pool. For example, during 1979 there were 200 cadaver kidneys retrieved among the six participating WATS centers. During the same period, 56 kidneys were retrieved at the OHSU. Our sensitized patients had access to approximately four times as many kidneys during 1979 as were available in our state.

The average survival (50 percent at 24 months) of the kidneys transplanted to the highly sensitized patients supports the concept that pretransplant sensitization to HLA antigens is not detrimental to early graft survival. Seven of the recipients were matched with their donors for two or fewer HLA-A and HLA-B antigens, and one was matched for three antigens. There were no matches for four antigens. Mismatched kidneys would not have been exported from one center to another for a patient with broadly reactive lymphocytotoxins under normal circumstances. Serum sharing thus provided access for these patients to kidneys that normally would not have been available to them.

The reasons for the discrepancies between the WATS tray crossmatch and the final crossmatch at the receiving center were unknown. Intervening blood transfusions, differences in crossmatching technique or problems with processing and distribution of the sera may all be contributory. Results of the crossmatches with unknown sera and cells sent to all participating centers last year indicate that standardization of crossmatching techniques may improve concordance among laboratories.

Regional kidney sharing programs are in operation in other parts of the United States and the world.[7-10] The largest and most successful regional programs in the United States are the New England Interhospital Organ Bank (IOB), the Southeastern Organ Procurement Foundation (SEOPF) and the Midwestern Organ Bank. The IOB operates with a central laboratory (the tissue typing laboratory at the Brigham and Women's Hospital) which collects sera and does tissue typing for all participating transplant centers (nine hospitals).

Kidneys or donor lymphocytes retrieved in the area are sent to the laboratory in Boston where crossmatches are carried out with patients' sera. The success of the IOB hinges on the central laboratory that does all of the crossmatches and allocates well-matched kidneys to patients in the area. SEOPF has 32 member laboratories and transplant programs. Kidney sharing is facilitated by the use of a central computer rather than a central laboratory. In the past, sera from all patients awaiting transplantation were distributed to all participating laboratories; however, as the number of patients in the region grew, this became cumbersome. In 1980 the laboratory in Nashville began collecting sera from highly sensitized patients only and now these sera are distributed to all laboratories for use in the crossmatch. The Midwest Organ Bank does tissue typing and crossmatching for four local transplant centers and exports kidneys to more distant centers. As with SEOPF, a computer facilitates organ sharing. Sera are not exchanged between the Midwest Organ Bank and distant transplant centers. Most regional kidney sharing programs conform to one of these three models.

The WATS program is smaller than these large regional programs and most closely resembles SEOPF, although greater distances separate participating centers. The geographic distance is a disadvantage but the smallness and spirit of cooperation optimize efficiency. The focus of this program has been on sharing kidneys for highly sensitized patients. If sharing of kidneys on the basis of A, B or DR antigen matching becomes a goal, the program will require computerization. Kidney sharing on the basis of HLA-A and HLA-B matching, however, may not be useful in the region.[11] The success of the WATS program should motivate transplant centers that are not involved to organize a regional program.

Summary

A regional kidney sharing program was formed in the far western United States by the Western Association of Transplant Surgeons (WATS). The purpose of this program was to locate cadaver kidneys for patients with broadly reactive lymphocytotoxic antibodies. The cadaver kidney pool available to these patients was increased significantly by providing sera from all patients to each participating transplant center to be used in crossmatches with all donors. Kidneys shared on the basis of a negative crossmatch at the retrieving center rather than antigen matching have been successfully grafted in 50 percent of cases. This successful program demonstrates the benefits of regional cooperation among transplant centers.

REFERENCES

1. Tilney NL, Strom TB, Carpenter CB, et al: The declining mortality rate in renal transplantation. N Engl J Med 299:1321-1325, 1978

2. Opelz G, Terasaki PI: Dominant effect of transfusions on kidney graft survival. Transplantation 29:153-158, 1980

3. McGeown MG, Douglas JF: Advantages of low dose steroids from the day after renal transplantation. Transplantation 29:287-289, 1980

4. Calne RY: Immunosuppression for organ grafting—Observations in cyclosporin A. Immunol Rev 46:113-124, 1979

5. Strober S, Slovin S, Gottlieb M, et al: Allograft tolerance after total lymphoid irradiation (TLI). Immunol Rev 46:86-112, 1979

6. Werner-Favre C, Jeannet M, Harder F, et al: Blood transfusions, cytotoxic antibodies and kidney graft survival—Preliminary results of a systematic transfusion protocol. Transplantation 28:343-346, 1979

7. Cockett ATK, Freeman RB: Regional sharing programs. SONY-W. NY St J Med 73:865-868, 1973

8. McCabe RE, Baker LN: New York-New Jersey regional transplant programs. NY St J Med 74:1405-1408, 1974

9. Hardie IR, Clune GJA: Exchange of cadaveric kidneys for transplantation in Australia and New Zealand. Aust NZ J Med 9:639-644, 1979

10. Terasaki PI, Langston M, Opelz G: Introduction: National kidney sharing and kidney preservation. Transplant Proc IX: 1493-1497, 1977

11. Barry JM, Craig DH, Fischer SM, et al: An analysis of 100 primary cadaver kidney transplants. J Urol 124:783-786, 1980

Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions of general interest are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. Each is sent to members of the appropriate Scientific Advisory Panel.* Their responses are collated, reviewed and then submitted to the Quality Care Review Commission as the Scientific Board's opinion on the scientific and practice aspects of the question. The Commission adds suggestions to assist peer review units and authorizes publication.*

These opinions and positions are informational only and are not intended to be used as instructions, directives or policy statements. The appropriateness of care in individual cases should not be determined by these answers, but should be reviewed by local peer review committees.

Questions and reprint requests may be submitted to the Medical Practice Questions Committee, Quality Care Review Commission, California Medical Association, 731 Market Street, San Francisco, CA 94103.

Radial Keratotomy

QUESTION:

Is radial keratotomy considered acceptable medical treatment for correction of myopia?

OPINION:

It is the unanimous opinion of the Advisory Panel on Ophthalmology that radial keratotomy is an experimental procedure. This panel also strongly advocates that radial keratotomy be done only with the approval and control of an investigational review committee.

Morbid Obesity

QUESTION:

(1) What are suitable guidelines for differentiating morbid from nonmorbid obesity in case selection for surgical relief?

(2) What are currently acceptable indications for gastroplastic surgery in the treatment of morbid obesity?

OPINION:

It is the opinion of the Advisory Panels on General Surgery and Internal Medicine that

(1) Morbid obesity may be defined using all of the following criteria:

(a) patient is more than 100 pounds overweight;

(b) prolonged attempts at dieting have not been successful;

(c) there are complications due to excessive weight; for example, respiratory insufficiency, hypertension, diabetes or psychosocial impairment.

(2) Currently acceptable indications for surgery include all of the following:

(a) patient is more than 100 pounds overweight;

(b) patient is between 18 and 50 years of age;

(c) absence of serious diseases contraindicating surgery;

(d) all methods of nonsurgical therapy have failed;

(e) surgical operation should be part of a comprehensive plan which includes preoperative and postoperative exercise, diet counseling and behavioral treatment.

Re-review of Mucous Membrane (Sublingual) Desensitization

QUESTION:

Is mucous membrane (sublingual) desensitization of proved therapeutic value in the treatment of allergy disorders?

OPINION:

The Advisory Panels on Allergy, General and Family Practice, and Otolaryngology believe that studies have reconfirmed that mucous membrane (sublingual) desensitization is not of proved therapeutic value in the treatment of allergy disorders.

Dimethyl Sulfoxide

QUESTION:

Is it acceptable medical practice to use dimethyl sulfoxide (DMSO) *in treatment of pain associated with arthritic conditions (or musculoskeletal pain)?*

*The Scientific Board of the California Medical Association has a Scientific Advisory Panel for each of 24 recognized specialties of medical practice. Each Advisory Panel includes representation from the appropriate department of each of the eight medical schools in California, representatives of specialty societies in the field and representatives from the Specialty Sections of the Association. The Advisory Panels are thus broadly and authoritatively based in both academia and practice.

OPINION:

It is the belief of the Advisory Panels on Orthopedics, Physical Medicine and Rehabilitation, Internal Medicine, Neurology and General Surgery that it is not acceptable medical practice. The use of DMSO for the purpose of relieving arthritis pain has not been approved by the Food and Drug Administration. Controlled studies have not yet been conducted which document the efficacy of using DMSO and delineate its toxicology.

Esterene

QUESTION:

Is the use of Esterene recognized as an accepted medical practice in the treatment of rheumatoid arthritis?

OPINION:

In the opinion of Advisory Panels on Internal Medicine and Orthopedics, there is no scientific evidence to support the use of Esterene, which is derived from cocaine, for the treatment of rheumatoid arthritis.

Radioallergosorbent Test (RAST)

QUESTION:

Is the radioallergosorbent test (RAST) *a recognized and effective allergy test?*

OPINION:

The Advisory Panels on Allergy, Internal Medicine, and Otolaryngology believe that the radioallergosorbent test (RAST) is a recognized and effective test. It is more expensive and less sensitive than direct skin testing. The majority of respondents think that RAST should be used for diagnosis in selected patients for whom skin testing is inappropriate or equivocal. Because of its expense, reasons for the use of RAST should be documented.

Paper Radioimmunosorbent Test (PRIST)

QUESTION:

Is the paper radioimmunosorbent test (PRIST) *a recognized and effective allergy test?*

OPINION:

In the opinion of the Advisory Panels on Allergy, Internal Medicine and Otolaryngology, the paper radioimmunosorbent test (PRIST) is a recognized and effective test for the determination of serum concentrations of IgE antibody and may be useful, together with other evidence, in the diagnosis of allergy. It should not be used routinely but rather in instances where there is some question about the diagnosis of allergy.

Singer-Blom Valve

QUESTION:

Is it accepted medical practice to perform the Singer-Blom valve operation for rehabilitation of laryngectomy patients?

OPINION:

The Advisory Panel on Otolaryngology is of the opinion that tracheoesophageal speech shunt procedures for vocal rehabilitation are accepted medical practice.

Clinical Ecology

QUESTION:

What is "clinical ecology"? Is this a recognized medical specialty?

OPINION:

It is the recommendation of the Advisory Panels on Allergy, Internal Medicine, Pediatrics, Preventive Medicine and Public Health and the Committee on Environmental Health, as well as the CMA Council, that "clinical ecology" is not a recognized medical specialty and does not have a single, standardized definition among medical practitioners.

Cytotoxic Testing for Food Allergy

QUESTION:

Is cytotoxic testing for food allergy considered acceptable medical practice?

OPINION:

It is the opinion of the Advisory Panel on Allergy that cytotoxic testing for food allergy has not been proved to be an effective or accepted medical practice and should be reserved for experimental use only.

BOOK REVIEWS

The journal does not review all books sent by the publishers. New books received are listed in the Advertising Section. Prices quoted are those given by the publishers.

SEXUAL REHABILITATION OF THE UROLOGIC CANCER PATIENT—Edited by Andrew C. von Eschenbach, MD, Department of Urology, and Dorothy B. Rodriguez, RN, MS, Department of Nursing, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston (02111), 1981. 322 pages, $39.95.

In the field of genitourinary cancer, urologists have certainly struggled. They have generally focused their efforts on early diagnosis, determination of the most effective and most appropriate treatment, and (it is to be hoped) the achievement of a long-range or complete cure—with as little morbidity and mortality as possible. Surgical procedures, radiation therapy, chemotherapy and hormone treatment all have a place, and beneficial combinations of treatment methods are aggressively sought and evaluated.

Discovery of cancer, eradication or suppression of the lesion and preservation of life are surely worthy goals. The authors and contributors to this volume successfully and significantly focus their attention on another vital aspect of the treatment of a patient with a genitourinary cancer—sexuality and its importance to emotional health and self-image. The segments of this book, we are told, were initially presented at a seminar entitled "Sexual Rehabilitation of the Urologic Cancer Patient" on May 4th and 5th, 1979, at the University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute in Houston, Texas.

There are sections on the physiology of normal male sexual function. The sexual impact of treatment is reviewed for cancer of the testis, penis, urethra, prostate and bladder. Emphasis, though, is placed upon rehabilitation of men made impotent by radical cystectomy or by radical prostatectomy or intensive external radiation therapy for prostatic carcinoma. The possible psychologic impediments of a urinary stoma in both sexes are well discussed. The use of penile prostheses, both inflatable and noninflatable, are well reviewed by Brantley Scott and Roy Finney.

The best part of this book is its approach to human sexuality, and its positive message applies to all of us—physicians, nurses, psychologists, counselors—as well as patients with urologic cancer. Sexuality is a part of one's humanity and personality, and it is much more than simply penile-vaginal intercourse. The sections on sexual counseling are excellent and imaginative. Patients need a frank discussion of the changes to be expected in their sexual function, but the authors point out the many forms of human sexuality and sexual expression and suggest a calm, positive and noncritical method of helping patients to find and express their own sexuality. Certainly trained stomal therapists and sexual therapists are useful members of the team. Their expertise is evident in this volume. Urologic surgeons cannot rely upon these experts entirely but must anticipate and deal with their patients' sexual rehabilitation themselves.

Sexual Rehabilitation of the Urologic Cancer Patient is a good review of normal and altered sexual function. Every urologic surgeon and urologic nurse would benefit from reading this useful and positive volume.

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* * *

RADIOLOGY OF THE PEDIATRIC ELBOW—Armand E. Brodeur, Michael J. Silberstein and E. Richard Graviss. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston (02111), 1981. 234 pages, $39.95.

This book should prove useful to all involved with the radiographic interpretation of the pediatric elbow, particularly those evaluating trauma. Its greatest value is as an atlas: the second chapter, the heart of the book, contains well-produced radiographs of the elbow from the newborn period through 16 years of age. Each illustration is accompanied by a concise valuable commentary. For example, the authors point out the "sliver" shape of the distal lateral humeral epicondylar growth center and the wide radiolucent interval between this center and the adjacent shaft; the normal position of the capitelar epiphysis in relation to the humerus and the shape of the intervening growth plate on the lateral view; and the bipartite appearance of the olecranon secondary growth center which may be mistaken for a fracture. Important points accompanying the illustrations are repeated when pertinent, which would allow for fast reference in an emergency room setting.

The first chapter, which precedes the atlas section, contains useful information related to the maturation sequence of the six centers of secondary ossification, emphasizing their variability in time of radiographic appearance and detailing the finer morphologic points of progressive maturation. The remaining chapters discuss elbow trauma of both hard and soft tissues, congenital abnormalities around the elbow joint, and hemophilia. Although this information is well covered in other sources, its inclusion in the text is useful as a convenient reference source.

The authors refer to the secondary centers of the medial and lateral distal humeral epicondyles and proximal ulna as epiphyses. Many would prefer the term apophyses for those secondary centers that serve as sites of ligamentous or muscular attachments.

The book is well written, is easy to read and is recommended as a handy reference for radiographic interpretation of trauma and as a source to complement the current atlas on the hand and wrist for evaluation of bone age.

MICHAEL J. PITT, MD
Associate Professor of Radiology
Associate Professor of Surgery (Orthopedics)
University of Arizona College of Medicine
Tucson, Arizona

in memoriam

California Medical Association

ALTHAUS, CHARLES F., Los Altos Hills. Died October 18, 1981, in Los Altos Hills of pancreatic cancer, aged 69. Graduate of the University of Buffalo School of Medicine, 1946. Licensed in California in 1956. Dr. Althaus was a retired member of the Santa Clara County Medical Society.

BAUER, EDWARD GREGORY, Fremont. Died October 10, 1981, in Fremont of amyotrophic lateral sclerosis, aged 56. Graduate of the University of Minnesota Medical School, Minneapolis, 1948. Licensed in California in 1952. Dr. Bauer was a member of the Alameda-Contra Costa Medical Association.

BEARD, HALLARD W., Castro Valley. Died October 24, 1981, aged 50. Graduate of the University of Illinois College of Medicine, Chicago, 1955. Licensed in California in 1976. Dr. Beard was a member of the Alameda-Contra Costa Medical Association.

CASE, JAMES ARTHUR, Inglewood. Died May 28, 1981, aged 57. Graduate of the University of Southern California School of Medicine, Los Angeles, 1949. Licensed in California in 1949. Dr. Case was a member of the Los Angeles County Medical Association.

CLARK, MARY H. (MARY H. CLARK BEEBE), San Jose. Died October 9, 1981, in Mountain View, aged 63. Graduate of the University of California Medical School, Berkeley-San Francisco, 1942. Licensed in California in 1942. Dr. Clark was a retired member of the Santa Clara County Medical Society.

DODGE, DOUGLAS RUDE, Pasadena. Died September 27, 1981, aged 73. Graduate of the University of Maryland School of Medicine, Baltimore, 1935. Licensed in California in 1936. Dr. Dodge was a member of the Los Angeles County Medical Association.

EISEN, EDWARD G., Los Angeles. Died April 20, 1981, aged 90. Graduate of the College of Physicians and Surgeons, Los Angeles, 1914. Licensed in California in 1914. Dr. Eisen was a retired member of the Los Angeles County Medical Association.

FRY, ARTHUR RAYMOND, JR, Morro Bay. Died October 7, 1981, in San Luis Obispo of lung cancer, aged 46. Graduate of the University of Oregon Medical School, Portland, 1962. Licensed in California in 1966. Dr. Fry was a member of the San Luis Obispo County Medical Society.

GRAY, CLAUDE C., Mendocino. Died October 31, 1981, in Mendocino of myocardial infarction, aged 68. Graduate of the University of Texas Medical Branch, Galveston, 1938. Licensed in California in 1944. Dr. Gray was a retired member of the Mendocino-Lake County Medical Society.

HAMILTON, ELEANOR B., El Cajon. Died October 31, 1981, aged 78. Graduate of the Western Reserve Medical University, Cleveland, 1929. Licensed in California in 1947. Dr. Hamilton was a retired member of the San Diego County Medical Society.

HONG, CHARLES JUAY, Bakersfield. Died October 3, 1981, in Bakersfield, aged 73. Graduate of the University of Michigan Medical School, Ann Arbor, 1937. Licensed in California in 1946. Dr. Hong was a member of the Kern County Medical Society.

IVERSON, JESSE J., San Francisco. Died October 2, 1981, in San Francisco, aged 73. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1938. Licensed in California in 1938. Dr. Iverson was a retired member of the San Francisco Medical Society.

KEELER, NELSON SHERMAN, SR., Piedmont. Died October 26, 1981, aged 80. Graduate of the University of Michigan Medical School, Ann Arbor, 1925. Licensed in California in 1929. Dr. Keeler was a member of the Alameda-Contra Costa Medical Association.

MACKLIN, EDWARD A., San Francisco. Died September 25, 1981, in Napa, aged 68. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1938. Licensed in California in 1939. Dr. Macklin was a member of the San Francisco Medical Society.

MCCORMICK, EDWARD W., Agnew. Died in March 1981 in Carmel, aged 80. Graduate of the University of Glasgow Medical Faculty, 1924. Licensed in California in 1948. Dr. McCormick was a retired member of the Santa Clara County Medical Society.

MUNCHHEIMER, KURT HEINZ, Rio Dell. Died September 15, 1981, in Rio Dell, aged 69. Graduate of the Goethe-Universität Medizinische Fakultät, Frankfurt, Germany, 1938. Licensed in California in 1953. Dr. Munchheimer was a retired member of the Humboldt-Del Norte Medical Society.

MURPHY, ELIZABETH A., Oakland. Died September 24, 1981, in Walnut Creek, aged 81. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Dr. Murphy was a retired member of the Alameda-Contra Costa Medical Association.

O'Brien, Thomas G., Santa Barbara. Died September 17, 1981, in Santa Barbara, aged 50. Graduate of the Jefferson Medical College, Philadelphia, 1956. Licensed in California in 1966. Dr. O'Brien was a member of the Medical Society of Santa Barbara County.

Paxman, Dalton G., jr., San Leandro. Died October 12, 1981, in San Leandro, aged 55. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1953. Licensed in California in 1954. Dr. Paxman was a member of the Alameda-Contra Costa Medical Association.

Pheasant, Homer C., Los Angeles. Died September 13, 1981, in Pasadena, aged 70. Graduate of the University of California Medical School, Berkeley-San Francisco, 1937. Licensed in California in 1944. Dr. Pheasant was a member of the Los Angeles County Medical Association.

Pryde, Arthur W., Saratoga. Died September 17, 1981, in Saratoga, aged 69. Graduate of the Western Reserve Medical University, Cleveland, 1937. Licensed in California in 1947. Dr. Pryde was a member of the Santa Clara County Medical Society.

Snodgrass, Wilfred J., Santa Monica. Died November 6, 1981, in Burlingame, aged 68. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1938. Licensed in California in 1942. Dr. Snodgrass was a member of the Los Angeles County Medical Association and served on the Editorial Board of The Western Journal of Medicine since 1977.

Sogemeier, Eberhard, San Mateo. Died May 11, 1981, aged 85. Graduate of Christian-Albrechts-Universität Medizinische Fakultät, Kiel, Prussia, 1921. Licensed in California in 1931. Dr. Sogemeier was a member of the San Mateo County Medical Society.

Stanghellini, Francis J., San Francisco. Died October 15, 1981, in Santa Rosa, aged 68. Graduate of the Creighton University School of Medicine, Omaha, 1937. Licensed in California in 1938. Dr. Stanghellini was a member of the San Francisco Medical Society.

Townsend, Lawrence D., Encinitas. Died September 14, 1981, in Eureka, aged 74. Graduate of the University of Oregon Medical School, Portland, 1948. Licensed in California in 1949. Dr. Townsend was a retired member of the San Diego County Medical Society.

Tyerman, Harry A., Bakersfield. Died November 3, 1981, in Bakersfield of heart failure, aged 75. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Dr. Tyerman was a retired member of the Kern County Medical Society.

Van Deventer, J. Kendall, Alhambra. Died March 3, 1981, in Alhambra, aged 73. Graduate of the Wash ington University School of Medicine, St. Louis, 1939. Licensed in California in 1942. Dr. Van Deventer was an associate member of the Los Angeles County Medical Association.

West, Keith Walter, Hayward. Died October 11, 1981, aged 59. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1947. Licensed in California in 1948. Dr. West was a member of the Alameda-Contra Costa Medical Association.

Williams, Barbara E., San Francisco. Died October 9, 1981, aged 66. Graduate of the University of California Medical School, Berkeley-San Francisco, 1948. Licensed in California in 1949. Dr. Williams was a member of the San Francisco Medical Society.

Zakoren, Peter M., Long Beach. Died July 28, 1981, aged 63. Graduate of the Aurora University Faculty of Medicine, Shanghai, 1941. Licensed in California in 1955. Dr. Zakoren was a member of the Los Angeles County Medical Association.

Utah State Medical Association

Mason, Reginald Gladstone, jr., Salt Lake City. Died October 20, 1981, in Salt Lake City, aged 48. Graduate of the University of North Carolina School of Medicine, Chapel Hill, 1962. Licensed in Utah in 1979. Dr. Mason was a member of the Salt Lake County Medical Society.

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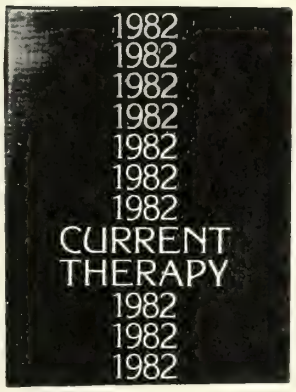

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(Continued on Page 42)

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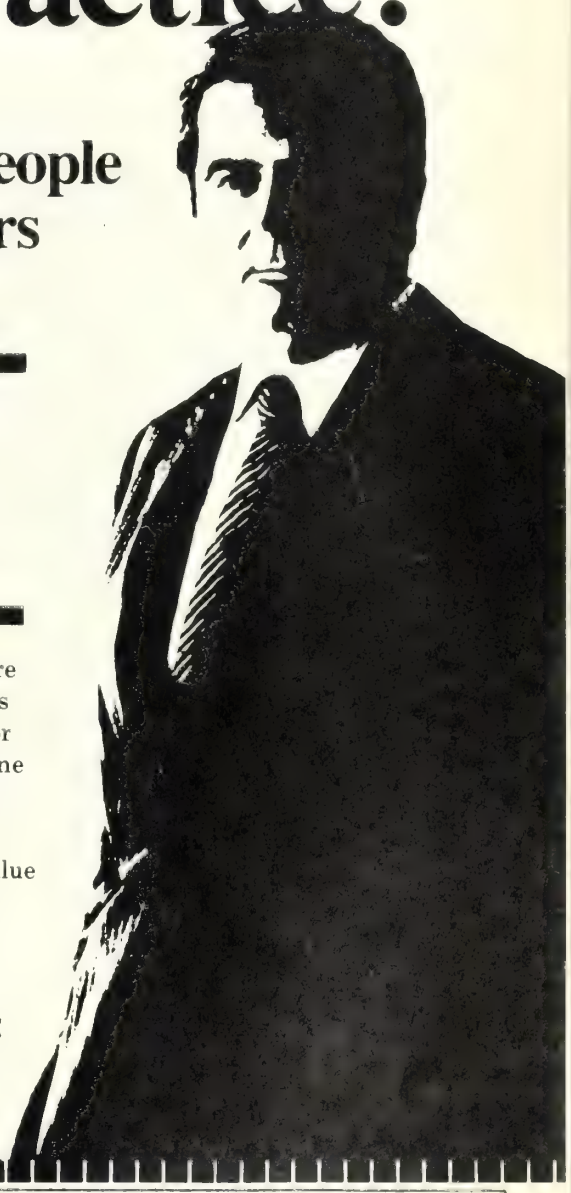

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(Continued from Page 29)

arch 20-24—**American Fertility Society.** See Of Interest To All, March 20-24.

arch 27-April 3—**Obstetrics and Gynecology.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

pril 2-3—**27th Annual T. Hart Baker, MD, Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at Hotel del Coronado, Coronado. Friday-Saturday. Contact: Lilia M. Guerrero, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

ay 10-12—**Recent Advances in OB/GYN.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 20 hrs. $300.

ne 2-5—**Controversies in Obstetrics and Gynecology.** Memorial Hospital Medical Center-UCI Center for Health Education at Silverado Country Club, Napa. Wednesday-Saturday. 20 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

EDIATRICS

bruary 16-19—**Clinical Investigation.** See Of Interest to All, February 16-19.

bruary 26-27—**New Directions in Care for the Handicapped Child.** State Dept. of Special Education and Calif. Chap. 1, American Academy of Pediatrics, at Children's Hospital Medical Center of Northern Calif., Oakland. Friday-Saturday. Contact: Peter Miller, MD, Marin Civic Ctr., Rm. 280, San Rafael 94903. (415) 499-6877.

arch 11-14—**Combined Southern California Pediatric Postgraduate Program.** Calif. Chap. 2, American Academy of Pediatrics; Los Angeles Pediatric Soc.; Children's Hosp. of Orange Co. and Southwestern Pediatric Soc. at Hilton Riviera, Palm Springs. Thursday-Sunday. Contact: Chalif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305.

arch 17-19—**General Pediatrics.** American Academy of Pediatrics at Royal Lahaina Resort, Maui. Wednesday-Friday. Contact: Dept. of Education, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

arch 20-25—**American Academy of Pediatrics—Spring Session.** Sheraton Waikiki, Honolulu. Saturday-Thursday. Contact: Dept. of Education, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

ril 10-17—**Pediatric Emergencies.** See Emergency Medicine, April 10-17.

ril 14—**Antibiotic Use in Pediatric Specialty Practice.** LLU. Wednesday. 4 hrs. $30.

ril 16-17—**New Directions in Care of the Handicapped Child.** American Academy of Pediatrics and Desert Hospital at Desert Hospital, Palm Springs. Friday-Saturday. 16 hrs. Contact: John Powers, AAP, P.O. Box 1034, Chicago 60602. (800) 323-0797.

ril 22-24—**Advances in Pediatrics.** UCSF. Thursday-Saturday. 18 hrs. $250.

ril 27-30—**7th Annual Symposium: Care of the Sick Newborn.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Tuesday-Friday. 19 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

y 1—**Pediatric Ophthalmology for the Primary Care Practitioner.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 6 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

y 3-7—**12th Annual Review of Pediatrics.** USC. Monday-Friday. 32 hrs. $350.

y 7-8—**Pediatric Nephrology.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

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May 19—**Los Angeles Pediatric Society—Annual Spring Meeting.** Hilton, Los Angeles. Wednesday. 2 hrs. $20. Contact: Eve Black, Exec. Sec., P.O Box 2022, Inglewood 90305. (213) 757-1198.

May 29-31—**Challenges in Pediatrics.** Northern California Chapter, American Academy of Pediatrics, at Monterey. Saturday-Monday. Contact: David A. Zlotnick, MD, 3200 Middlefield Rd., Palo Alto 94306.

July 11-12—**First Annual Disneyland Pediatric Seminar.** American Academy of Pediatrics, Calif. Chap. 2, at Disneyland Hotel, Anaheim. Sunday-Monday. 12 hrs. Contact: AAP, Calif. Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

PSYCHIATRY

February 19-20—**Heinz Von Foerster on Cybernetics, Language and Understanding.** Mental Research Institute, Palo Alto. Friday-Saturday. 12 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 26-27—**The Use of Drugs in the Treatment of Patients With Psychiatric Disorders.** UCLA at VA Medical Center, Brentwood. Friday-Saturday. 6 hrs. $75.

February 27-28—**Biobehavioral Science for Psychiatrists.** STAN. Saturday-Sunday. 12 hrs. $225.

March 12-14—**Short-Term Dynamic Psychotherapy.** UCSD at Hilton, San Diego. Friday-Sunday. 24 hrs. $275.

March 27—**Reconsiderations of Psychoanalytic Listening.** Southern California Psychoanalytic Society at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Mrs. Carol Ziff, Exec. Sec., So. Calif. Psychoanalytic Soc., 9024 Olympic Blvd., Beverly Hills 90211. (213) 936-2877.

March 29-April 3—**American Orthopsychiatric Association—59th Annual Meeting.** Hilton, San Francisco. Monday-Saturday. Contact: AOA, 1775 Broadway, New York 10019. (212) 586-5690.

April 23-24—**Psychotherapy and Law Enforcement: Issues and Techniques.** UCSF at Hyatt Regency, San Francisco. Friday-Saturday. Contact: Aveleen Blumenstock, Asst. Dir. of Cont. Ed., Dept. of Psychiatry, UCSF, Langley Porter Institute, Box 2D, 401 Parnassus Ave., San Francisco 94143. (415) 681-8080, ext. 554.

June 3-5—**Depression.** UCD at Del Monte Hyatt, Monterey. Thursday-Saturday.

June 21-25—**Comparative Psychotherapies.** USC at San Diego. Monday-Friday. 21 hrs. $295.

RADIOLOGY AND PATHOLOGY

March 3-5—**Sierra Radiology Conference—3rd Annual.** Sacramento Radiology Research and Education Fndn. and No. Calif. Radiological Soc. at North Lake Tahoe. Wednesday-Friday. 18 hrs. $265. Contact: Michael H. Reid, PhD, MD, Sac. Rad. Research and Ed. Fndn., P.O. Box 161112, Sacramento 95816.

March 4-5—**Pathology of Parasitic Infections.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 17 hrs. Contact: Asst. Dir., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 15-18—**International Workshop on Physics and Engineering in Medical Imaging.** UCI at Asilomar Conference Center, Pacific Grove. Monday-Thursday.

March 15-19—**Diagnostic Radiology.** UCSF. Monday-Friday. 33 hrs. $375.

March 24-26—**Gram Negative Organisms: An Approach to Identification.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 20 hrs. Contact: Asst. Dir., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 11-15—**Postgraduate Course in Diagnostic Radiology.** Memorial Hospital Medical Center-UCI Center for Health Education at Disneyland Hotel, Anaheim. Sunday-Thursday. 24 hrs. Contact: Asst. Dir., UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 15-17—**Tumor Labelling Microcellular: Theory and Clinical Application.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Saturday. 17 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 7-8—**Common Nervous System Pathology Diagnosis and Treatment.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 14 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 20-25—**Pathology of the Lung.** UCSD at La Jolla Village Inn, La Jolla. Sunday-Friday. 50 hrs.

July 24-August 1—**Diagnostic Radiology: An In-Depth Seminar Approach to Diagnostic Imaging.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. 9 days. 24 hrs. $345.

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SURGERY

February 18-21—**Pathophysiology and Techniques of Cardiopulmonary Bypass: II.** Cardiothoracic Research and Education Fndn. and Vascular Disease Fndn. at Hilton on Mission Bay, San Diego. Thursday-Sunday. Contact: CREF, P.O. Box 33185, San Diego 92103.

February 26-27—**Ender Nailing: A Motor Skills Course With Hans Ender, MD.** UCD. Friday-Saturday. 11 hrs. $200.

February 28-March 4—**Lake Tahoe Vitreo-Retinal Symposium.** Retinal Faculty, UCD, at Granlibakken Ski Resort, Tahoe City. Sunday-Thursday. Contact: Donald May, MD, 2315 Stockton Blvd., Sacramento 95817. (916) 453-2941.

March 1-5—**Surgical Forum.** Society of Graduate Surgeons at Ambassador Hotel, Los Angeles. Monday-Friday. 31 hrs. $350. Contact: Dir. of Med. Ed., Society of Graduate Surgeons, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 4-5—**13th Annual Lecture and Postgraduate Seminar—Pediatric Ophthalmology and Strabismus Update.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

March 5-10—**23rd Clinical Congress of Abdominal Surgeons.** American Society of Abdominal Surgeons at Caesars Palace, Las Vegas. Friday-Wednesday. 20 hrs. $150, members; $200, nonmembers. Contact: Blaise F. Alfano, MD, Exec. Sec., 675 Main St., Melrose, MA 02176. (617) 665-6102.

March 12—**Male Infertility Seminar.** Western Section, American Urological Assn., at Marriott, Los Angeles. Friday. Contact: Kathy De Santis, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

March 18-19—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

March 25-27—**Diagnosis and Treatment of Retinal, Macular and Vitreous Diseases.** Retina Research Fund of St. Mary's Hospital and Medical Center at Silverado Country Club, Napa. Thursday-Saturday. $225. Contact: Howard Schatz, MD, Retina Research Fund of St. Mary's Hosp., 450 Stanyan St., San Francisco 94117. (415) 921-4860.

March 28-31—**19th Annual Seminar on Controversial Areas in Surgery.** UCLA at Palm Springs. Sunday-Wednesday.

March 29-April 2—**Management of Coronary Heart Disease: Medical, Surgical, Exercise.** See Medicine, March 29-April 2.

March 31-April 4—**10th Annual Symposium on Vascular Surgery.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Sunday. $385.

April 2—**Anterior Vitrectomy—1982.** Sutter Community Hospitals at Sutter General Hospital, Sacramento. Friday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

April 15-17—**Postgraduate Course in General Surgery.** UCSF. Thursday-Saturday.

April 17-24—**Frontiers in Functional Neurosurgery.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 21-23—**American Intra-Ocular Implant Society.** Century Plaza, Los Angeles. Wednesday-Friday. Contact: AIOIS, P.O. Box 3140, Santa Monica 90403. (213) 829-7317.

April 23-24—**Vitrectomy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

April 24-May 1—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $325.

April 25-29—**American Association of Neurological Surgeons.** Honolulu. Sunday-Thursday. 40 hrs. Contact: Selene Patterson, AANS, 625 N. Michigan Ave., Suite 1519, Chicago 60611. (312) 944-4205.

May 2-6—**American Society of Colon and Rectal Surgeons—Annual Convention.** San Francisco. Sunday-Thursday. 20 hrs. $125, members: $135, nonmembers. Contact: Harriette Gibson, Admin. Sec., ASCRS, 615 Griswold, Suite 516, Detroit 48226. (313) 961-7880.

May 11-14—**3rd Annual Verne T. Inman/17th Annual LeRoy C. Abbott Lectureship.** UCSF. Tuesday-Friday. 14 hrs.

(Continued on Page 48)

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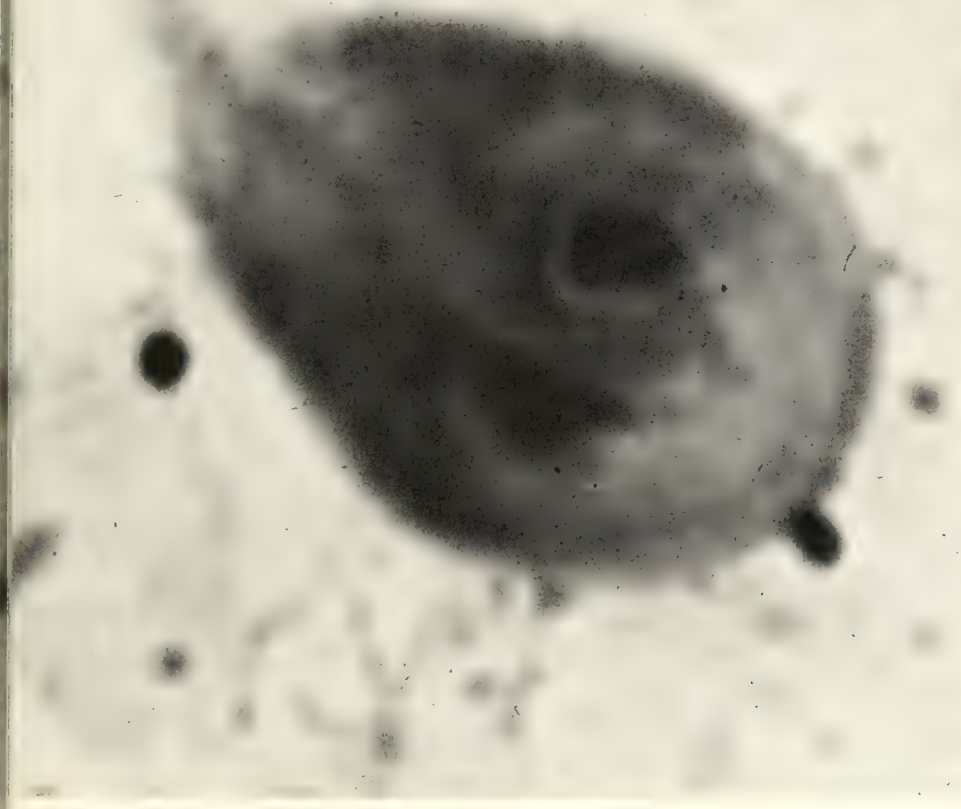

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Rosenthal, P., and Liebman, W.M: Comparative study of stool examinations, duodenal aspiration, and pediatric Entero-Test for giardiasis in children. *J. PEDIAT. 96:* 278 (Feb.) 1980.

Thomas, G. E., et al: Use of the Entero-Test duodenal capsule in the diagnosis of giardiasis. *South Afr. Med J. 48:* 2219, 1974.

Lopez, M. E., et al: Infeccion duodeno-yeyunal en el niño con desnutricion energetico-proteinica. *Rev. Med. Hosp. Nat. Niños 13:* 53, 1978.

Gilman, R. H: Identification of gall typhoid carriers by a string bladder device. *The Lancet:* April 14, p. 795, 1979.

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(Continued from Page 46)

Contact: Eileen Gaines, Alumni Sec., UCSF Dept. of Orthopedic Surgery, U471, San Francisco 94143. (415) 666-1166.

May 12—**Surgical Subspecialties.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Secretary, Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

May 14-15—**Diagnostic Ocular and Orbital Ultrasound Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $125. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

June 3-4—**12th Annual Neurosurgery Postgraduate Course.** UCSF at Hilton, San Francisco. Thursday-Friday. 16 hrs. $250.

June 4-7—**Intensive Course in Refractive Keratoplasty: Barraquer Technique.** Jules Stein Eye Institute, Los Angeles. Friday-Monday. 32 hrs. $1,750. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

June 19-26—**Ophthalmology.** USC at Hawaii. One week. 28 hours. $425.

August 12-14—**Selection and Technique for Use of Muscle and Musculocutaneous Flaps in Reconstructive Surgery.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 20 hrs. $420.

OF INTEREST TO ALL PHYSICIANS

February 16-19—**Clinical Investigation.** Western Section of Am. Federation for Clinical Research, Western Soc. for Clinical Research, Western Section of Soc. for Investigative Dermatology, Western Soc. for Pediatric Research, and UCSF at Carmel. Tuesday-Friday. 20 hrs. $25, nonmembers + $10 for CME certificate. Contact: Allen D. Cooper, MD, Room S-069, Stanford Med Ctr., Stanford 94305.

February 16-June 8—**Family Practice.** USC. Tuesday evenings. $395.

February 18-19—**Hospital Epidemiology for Physicians and Infection Control Teams.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. Contact: Richard P. Henke, MD, Memorial Hosp., 2801 Atlantic Ave., Long Beach 90801. (213) 595-2431, ext. 23.

February 20-21—**Ninth Annual Family Practice Symposium.** So. Calif. Permanente Medical Group at Marriott, Anaheim. Saturday-Sunday. Contact: Dana Reisman, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-7070.

February 22—**Symposium on Geriatric Medicine.** Sutter Community Hospitals at Red Lion Motor Inn, Sacramento. Monday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

February 22-25—**Critical Care Medicine—20th Annual Symposium.** USC at MGM Grand, Las Vegas. Monday-Thursday. 28 hrs. $295.

February 22-26—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $325.

February 25-28—**8th Annual Basic, Intermediate and Advanced Workshops in Clinical Hypnosis.** UCI and Southern Calif. Society of Clinical Hypnosis at The Grand Hotel, Anaheim. Thursday-Sunday. 28 hrs. Contact: So. Calif. Soc. of Clinical Hypnosis, 4454 Van Nuys Blvd., Suite 215, Sherman Oaks 91403. (213) 872-3350.

March 1-2—**Treatment Issues in Geriatrics.** Western Gerontological Society and Washington State Psychiatric Assn. at Town and Country Hotel, San Diego. Monday-Tuesday. Contact: Barbara Freda, WGS, 785 Market St., Suite 1114, San Francisco 94103. (415) 543-2617.

March 5-6—**Advances in Alcoholism—Third Annual Symposium.** Raleigh Hills Foundation and American Medical Society on Alcoholism at Registry Hotel, Newport Beach. Friday-Saturday. $200. Contact: Kim Hilberg, Raleigh Hills Fndn., 17861 Cartwright Rd., Irvine 92714. (714) 641-1616.

March 5-11—**Annual Postgraduate Convention—Primary Care Update.** LLU School of Medicine Alumni Assn. at LLU. One week. Contact: Beverly Hardt, 11245 Anderson St., Suite 200, Loma Linda 92354. (714) 824-4633.

March 8-12—**Sports Medicine.** Northwestern Univ. Center for Sports Medicine at Maui. Monday-Friday. 25 hrs. Contact: Bates Noble, MD, Northwestern Univ. Ctr. for Sports Medicine, 303 E. Chicago Ave., Chicago 60611.

March 10—**Pain Management.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

March 10-13—**Optimal Health: A Guide for Practicing Physicians.** Scripps Clinic and Research Fndn. at La Costa Resort Hotel, Carlsbad. Wednesday-Saturday. 22 hrs. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

March 12-17—**California Medical Association—111th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Joan Kammerer, CMA.

March 13—**Hepatitis: A Sexually Transmissible Disease.** UCLA. Saturday. 6 hrs. $65.

March 13-20—**Reproductive Endocrinology, Infertility and Contraception.** USC at Maui. One week. $395.

March 15-19—**Sports Medicine.** Univ. of Hawaii at Princess Kaiulani Hotel, Waikiki, Honolulu. Monday-Friday. 18 hrs. $250. Contact: Joy Lewis, Box CE-CCECS, 2530 Dole St., Honolulu 96822. (808) 948-8244.

March 18-21—**Clinical Management.** STAN at The Lodge, Pebble Beach. Thursday-Sunday. 12 hrs. $175.

March 19—**Diabetes and Nutrition Update.** UC and STAN at Hilton, San Francisco. Friday. Contact: UCD.

March 19-21—**In Pursuit of Wellness.** UCSF at Jack Tar Hotel, San Francisco. Friday-Sunday. $75. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

March 20-24—**American Fertility Society—38th Annual Meeting and 15th Postgraduate Program.** MGM Grand, Las Vegas. Saturday-Wednesday. Contact: Herbert H. Thomas, MD, Med. Dir., AFS, 1608 13th Ave. S., Suite 101, Birmingham, AL 35256. (205) 933-7222.

March 20-27—**Medical Genetics for Health Professionals.** San Jose State University. One week. 15 hrs. Contact: Kate Wright-Rodgers, MPH, Cont. Ed., San Jose State Univ., Washington Square, San Jose 95192. (408) 277-3778.

March 25-26—**Common Problems in Office Practice.** LLU at Casa Royale Motor Inn, Bakersfield. Thursday-Friday. 6 hrs.

March 25-27—**Third Annual Dermatology Conference: Dermatology for Non-Dermatologists.** Eisenhower Medical Center and Stanford at Annenberg Center for Health Sciences, Eisenhower Med. Ctr., Rancho Mirage. Thursday-Saturday. Contact: P. Kokemueller, MS, Conf. Services Mgr., Annenberg Ctr. for Health Sciences, Eisenhower Med. Ctr., 39000 Bob Hope Dr., Rancho Mirage 92270.

March 27-April 3—**Otolaryngology for Non-Otolaryngologists.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 3-10—**Topics in Family Practice.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 10-17—**Management of Pain.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 22-24—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 22-25—**Wound Management.** UCSD at Hilton, San Diego. Thursday-Sunday. 20 hrs.

April 22-25—**Mountain Medicine.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Friday-Sunday. 19 hrs.

May 1-8—**Diagnostic and Therapeutic Skills.** USC at Hawaii. One week. 29 hrs. $425.

May 2-5—**Medical Evaluation of the Preoperative Patient.** UCD at Del Monte Hyatt, Monterey. Sunday-Wednesday. 17 hrs. $245.

May 2-5—**American Medical Informatics Association Congress 82—First Annual Joint Conference.** AMIA, Soc. for Advanced Medical Systems, Soc. for Computer Medicine, Internat'l Health Evaluation Assn., Salutis Unitas, Univ. of Missouri-Columbia Health Care Technology Ctr., IL Conf. on Medical Information Systems, at Hyatt on Union Square, San Francisco. Sunday-Wednesday. Contact: M. F. Collen, MD, 3451 Piedmont Ave., Oakland 94611.

May 3-7—**Symposium on Non-Emergent Outpatient Care.** UCSD at Hilton, San Diego. Monday-Friday. 27 hrs. $325.

May 3-9—**Basic Diving Medicine.** UCSF at Fresno. One week. Contact: Vincent S. O'Hara, MD, VA Medical Center, 2615 E. Clinton, Fresno 93703. (209) 225-6100, ext. 345.

May 9-14—**Fingers-to-Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Friday. 40 hrs. $375.

May 12—**Common Fractures.** LLU. Wednesday. 4 hrs. $30.

May 22-23—**Conference on Health Problems Related to the Chinese in America.** Chinese Hospital and UCSF at Holiday Inn/Financial District, San Francisco. Saturday-Sunday. 12 hrs. $85. Contact: Elizabeth S. Weston, Chinese Hosp., 845 Jackson St., San Francisco 94133. (415) 982-2400, ext. 215.

May 31—June 4—**9th Annual Joint UCLA-Santa Monica Hospital Medical Center Family Practice Refresher Course.** Miramar-Sheraton, Santa Monica. Monday-Friday. 35 hrs. Contact: UCLA.

June 9-11—**7th Annual Conference: Clinical Application of Hyperbaric Oxygen.** Memorial Hospital Medical Center at Disneyland Hotel, Anaheim. Wednesday-Friday. 24 hrs. Contact: Baromedical Dept., Memorial Hosp. Med Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3613.

June 14-19—**UCI Family Practice Refresher Course.** Marriott, Newport Beach. Sunday-Friday. 50-56 hrs.

July 6-8—**Family Practice Board Review Course.** UCSF. Tuesday-Thursday.

July 9-11—**Sensory Systems' Influence on Movement and Tone—10th Annual Sensorimotor Integration Symposium.** UCSD at Holiday Inn at the Embarcadero, San Diego. Friday-Sunday.

August 12-13—**National Institute for Care of the Elderly.** Univ. of Nevada-Reno School of Medicine at MGM Grand, Reno. Thursday-Friday. 12 hrs. Contact: Leanne Stone, Cont. Ed., Univ. of Nevada-Reno, Reno 89557. (702) 784-4046.

August 13-14—**6th Annual Sports Medicine Conference.** Univ. of Nevada-Reno School of Medicine at MGM Grand, Reno. Friday-Saturday. 12 hrs. Contact: Leanne Stone, Cont. Ed., Univ. of Nevada-Reno, Reno 89557. (702) 784-4046.

August 16-20—**Advanced Diving Medicine.** UCSF at San Diego. Monday-Friday.

August 23-September 3—**Intensive Residency in Occupational Medicine, Session. I.** UCSF at Golden Gateway Holiday Inn, San Francisco. 12 days. 80 hrs. $1,000.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA

No courses announced.

IDAHO

See Washington Listings, February 13, March 6-13, March 15, April 19, May 29 and June 14.

MONTANA

March 20-March 27—**Pulmonary Diseases: A Practical Approach.** Big Sky. Saturday-Saturday. 20 Category I credit hours; also 20 AAFP Elective hours, and 20 ACEP hours. Fee: $260 for Physicians; $180 for Physicians Assistants, Interns and Residents. Contact: M. S. M. Watts, MD, Associate Dean and Director, University of California, San Francisco, Extended Programs in Medical Education, San Francisco, CA 94143. Telephone—For Registration: (415) 666-2894 or 666-2483; for Program Information: (415) 666-4251.

April 15-17—See Washington Listings.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, P.O. Box 9366, Albuquerque, NM 87119 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 247-0539.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

(Continued on Page 51)

oncology update 82

Urban
Prosnitz
Livingston
Wellisch
Mitchell
Carter

Saturday, April 3, 1982
8:30 a.m.–5:00p.m.
The Biltmore Hotel
Los Angeles, California

Presented by
Northridge Hospital
Clinical Center for
Cancer and Blood Disease

In Cooperation with the
American Cancer Society

This is an approved program of Continuing Medical Education. Physicians attending this course may report up to eight (8) hours of Formal (Category I) credit toward the California Medical Association Certificate in Continuing Medical Education.

This course has been approved for 8 hours by the California Board of Registered Nursing Provider Number 00121.

A Program for
Physicians, Nurses, and
Allied Health Professionals

For Further Information
Call (213)885-5311

Mail to NHMC Department of Medical Education
18300 Roscoe Boulevard, Northridge, California 91328
Physicians $125.00. All others $45.00.

Name

Address

City

State

Zip

(Continued from Page 49)

February 22-26—**Taos Medical Symposium—Sports Medicine.** Taos. Monday-Friday. Kachina Lodge. 18 credit hours, also AAFP Prescribed. Contact: Dale A. Gray, MD, Taos Medical Symposium, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

February 26-28—**10th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Kachina Lodge. 13 credit hours, also AAFP Prescribed. Contact: American Lung Association of New Mexico, 216 Truman NE, Albuquerque, NM 87108. (505) 265-0732.

March 6—**Wylder Lecture "Sleep and Sleep Disorders in Infants and Children."** Albuquerque. Saturday. UNM Nursing/Pharmacy Building, North Campus. 4 credit hours. Contact: Robert Tully, MD, 8014 Aspen NE, Albuquerque, NM 87110. (505) 298-2236.

March 8-10—**New Mexico Metabolism Seminar.** Taos. Monday-Thursday. Tennis Ranch. 15 credit hours. Contact: Martin J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd. SE, Albuquerque, NM 87108. (505) 842-7000.

March 13—**Infectious Disease Update Seminar.** Albuquerque. Saturday. Four Seasons Motor Inn. 7½ credit hours, also AAFP Prescribed. Contact: Martin J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd. SE, Albuquerque, NM. (505) 842-7000.

March 16-21—**Purgatory Medical Ski Symposium.** Durango, Colorado. Tuesday-Sunday. Iron Horse Resort & Convention Center. 24 credit hours, also AAFP Prescribed. Contact: David R. Holten, MD, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

March 18-19—**Advanced Trauma Life Support Provider's Course.** Albuquerque. Thursday-Friday. UNM Family Practice Building. 16 hours credit, also AAFP Prescribed. Contact: William Schiller, MD, Director, Burn & Trauma Unit, UNM Hospital, Albuquerque, NM 87131. (505) 843-2231.

March 30-31—**Base Station Physician Course.** Taos. Tuesday-Wednesday. Sagebrush Inn. 9 credit hours, also AAFP Prescribed. Contact: Arleen L. Sadowsky, MD, President, NM Chapter American College of Emergency Physicians, 6320 Palma Pl. NW, Albuquerque, NM 87120.

April 1-3—**New Mexico Chapter, American College of Emergency Physicians Meeting.** Taos. Thursday-Saturday. Sagebrush Inn. 18 credit hours, also AAFP Prescribed. Contact: Arleen L. Sadowsky, MD, President, 6320 Palma Pl. NW, Albuquerque, NM 87120.

April 23-24—**Geriatrics Medicine Update—1982.** Albuquerque. Friday-Saturday. AMFAC Hotel. 10 credit hours, also AAFP Prescribed. Contact: UNM School of Medicine, Office of CME, Albuquerque, NM 87131. (505) 277-3942.

May 5-7—**New Mexico Medical Society Annual Meeting.** Santa Fe. Wednesday-Friday. Hilton Inn. 10 credit hours, also AAFP. Contact: NMMS, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

May 14-15—**15th Annual OB/GYN Update.** Albuquerque. Friday-Saturday. AMFAC Hotel. 10 credit hours, also AAFP Prescribed. Contact: UNM School of Medicine, Office of CME, Albuquerque, NM 87131. (505) 277-3942.

June 17-19—**Radiology for Family Physicians 1982—An Update.** Santa Fe. Thursday-Saturday. Symposia de Santa Fe. 15 credit hours, also AAFP Prescribed. Contact: Marcus J. Smith, MD PO Box 5175, Santa Fe, NM 87501. (505) 982-5218.

July 8-10—**25th Annual Meeting, New Mexico Ophthalmological Society.** Santa Fe. Thursday-Saturday. Hilton Inn. 8 credit hours. Contact: Walter J. Levy, MD, 465 St. Michael's Dr., Santa Fe, NM 87501. (505) 982-1911.

July 19-22—**25th Annual Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 credit hours. Also AAFP Prescribed. Contact: Convention Director, NM Academy of Family Physicians, PO Box 456, Sunland Park, NM 88063. (505) 247-0539 or (915) 533-3449.

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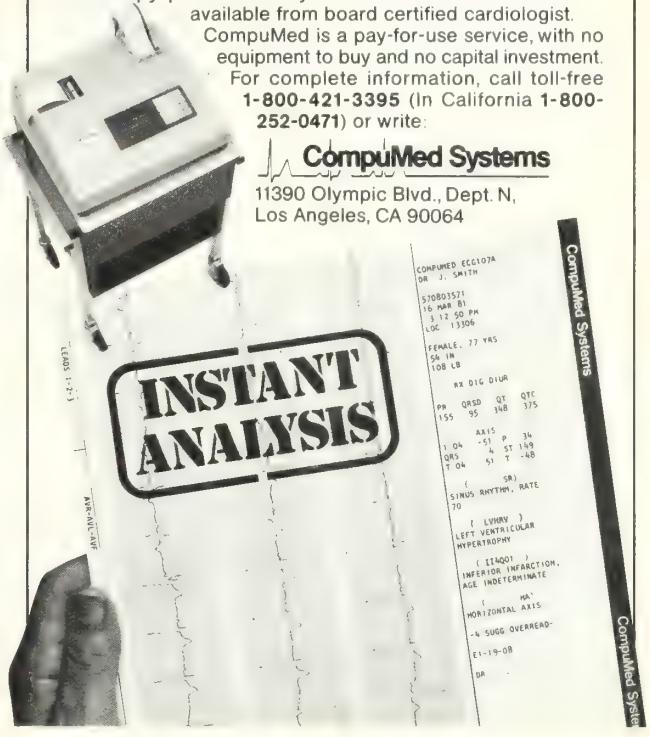

July 23-25—**11th Annual Santa Fe Cardiology Symposium.** Santa Fe. Friday-Sunday. Inn at Loretto. 14 credit hours, also AAFP Prescribed. Contact: Meeting Director, Southwest Cardiology Associates, 8100 Constitution NE, Albuquerque, NM 87110. (505) 292-1114.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

MKSAP V REVIEW

(Sponsors: Utah Region, American College of Physicians/Utah Society of International Medicine/University of Utah)
University Medical Center, Salt Lake City

October 1981-June 1982 (Ongoing)—Thursdays. 2 hrs. Fee for Optional Materials: $160 (ACP non-members); $60 (ACP members). Contact: John Holbrook, MD (801) 581-7818.

* * * *

February 12-16—**27th Annual Postgraduate Course in Anesthesiology: Anesthesiology and the Lung** (Sponsor: University of Utah). Salt Lake City. Friday-Tuesday. Hotel Utah. 17 hrs. Fee: $250. Contact: T. Stanley, MD (801) 581-6393.

February 15-19—**Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Park City. Monday-day-Friday. Holiday Inn. 25 hrs. Fee: $300. Contact: John Matsen, MD (801) 581-5514.

February 17-20—**Occupational and Clinical Problems in Exercise Limitation** (Sponsor: Intermountain Thoracic Society). Salt Lake City. Wednesday-Saturday. Little America Convention Center. 20 hrs. Fee: Members, $75, Non-members, $100, Allied Health Workers, $25. Contact: Franklin K. Brough, PhD (801) 484-4456.

February 20-23—**23rd Annual OB/GYN Course** (Sponsor: University of Utah). Park City. Saturday-Tuesday. The Yarrow. 14 hrs. Fee: $275. Contact: David Engleberg (801) 581-3087.

February 20-27—**The Snowbird Conference on Modern Diagnostic Methods in Internal Medicine** (Sponsors: George Washington University Medical Center, Washington, DC/ Academy of Continuing Medical Education, Salt Lake City). Snowbird. Saturday-Saturday. 15 hrs. Fee: $245 (Residents: $150). Contact: Gregg P. Thomas, CME Office, George

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

Washington University Medical Center, 2300 Eye Street, NW, Washington, DC 20037. (202) 676-4285.

February 24-26—**Training and Certification for Pulmonary Function Testing (Spirometry)** (Sponsors: University of Utah/Rocky Mountain Center for Occupational and Environmental Health). Park City. Wednesday-Friday. The Yarrow. 18 hours. Fee: $350. Contact: Ms. K. Blosch (801) 581-5710.

February 24-27—**Reproductive Endocrinology and Infertility Update** (Sponsor: University of Utah). Park City. Wednesday-Saturday. The Yarrow. 14.5 hrs. Fee: $275. Contact: David Engleberg (801) 581-3087.

March 1-3—**Common Problems in Pediatrics—Intermountain Pediatric Society Annual Scientific Meeting** (Sponsor: University of Utah). Salt Lake City. Monday-Wednesday. Little America. 15 hrs. Fee: $190. Contact: Jacque Bachtell (801) 581-3729.

March 1-5—**7th Annual Advances in Internal Medicine** (Sponsor: University of Utah). Snowbird. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 6-13—**4th Annual Park City Radiology Conference** (Sponsor: University of Utah). Park City. Saturday-Saturday. Holiday Inn. 20 hrs. Fee: $290. Contact: P. Ruben Koehler, MD (801) 581-8188.

March 8-12—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Snowbird. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 13-20—**First Annual Oculo-Plastic SRI Meeting** (Sponsor: University of Utah). Park City. Saturday-Saturday. 15 hrs. Fee: $225. Contact: Darrel Wolfley, MD (801) 363-3355.

March 15-19—**Second Annual Nutrition in Contemporary Medicine Course** (Sponsor: University of Utah). Park City. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 18-19—**Infection Control Update—Rocky Mountain Infection Control Association (RMICA)** (Sponsor: University of Utah). Salt Lake City. Thursday-Friday. Little America. 12 hrs. Fee: $75. Contact: Sego Matsumiya (801) 582-1565.

March 21-28—**Park City Dermatological Seminar** (Sponsors: St. Mark's Hospital, University of Utah, Intermountain Dermatology Foundation [IDF]). Park City. Sunday-Sunday. Shadow Ridge Condo Hotel. 20 hrs. Fee: $250. Contact: IDF, 1151 East 3900 South, Salt Lake City 84117 (801) 268-0435.

March 24-25—**Genetics: Impact of Genetic Disorders on the Family** (Sponsor: University of Utah). Salt Lake City. Wednesday-Thursday. University of Utah Medical Center. 12 hrs. Fee: $50-$65. Contact: John Carey, MD, (801) 581-8943.

March 26-27—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

March 27-28—**The Complexities of Interpreting CT Scans in Cervical and Lumbar Disc Disease** (Sponsors: Western Neurological Associates/St. Mark's Hospital). Salt Lake City. Marriott Hotel. Monday-Tuesday. 10 hrs. Fee: $225. Contact: Linda June Krueger (801) 262-3441.

April 7-9—**Health Hazards of Minerals and Mining: 4th Annual Park City Environmental Health Conference** (Sponsors: University of Utah/Rocky Mountain Center for Occupational and Environmental Health). Park City. Monday-Wednesday. 24 hrs. Fee: $300. Contact: Katharine Blosch (801) 581-5710.

April 15-17—**First Annual Clinical Ophthalmology Meeting at Snowbird** (Sponsor: University of Utah). Snowbird. Tuesday-Thursday. 9 hrs. Fee: $50. Contact: Rebecca Olsen (801) 581-6384.

May 14-15—**Advanced Trauma Life Support** (Sponsor: Uni-

The Community Cancer Center of

THE HOSPITAL of the GOOD SAMARITAN

presents

Advances in Cancer Detection

THE NINTH ANNUAL SYMPOSIUM

Wednesday

FEBRUARY 17, 1982

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EMERSON DAY, MD ..... *Chicago, IL*
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WILLIAM H. KERN, MD ..... *Los Angeles, CA*
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This course is acceptable for up to 7 hours Category I Credit towards CMA and AMA certificates in Continuing Medical Education.

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For More Information:

Bonnie VanWaardenburg
Coordinator of Symposia
(213) 977-2345

versity of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

June 11-12—**Medical Aspects of Laser Surgery** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Little America. Credit and fee to be announced. Contact: John Dixon, MD (801) 581-8201.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

February 13-20—**(HAWAII) Plastic Surgery.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

February 13-20—**(IDAHO) Infectious Diseases.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

February 16—**Cardiology 1982.** Seattle. Tuesday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital, Education and Training Department, 1551 North 120th, Seattle, WA 98133. (206) 364-0500, ex: 1737.

February 17—**Advances in Diabetes.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

February 17—**(MONTANA) Laboratory/Clinical Management Rheumatologic Disorders.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

February 18—**(MONTANA) Laboratory/Clinical Management Rheumatologic Disorders.** Billings. Thursday. Marillac Hall. Contact: U/W.

February 18-19—**Sports Medicine in the Emergency Room.** Wenatchee. Thursday-Friday. Thunderbird Motor Inn. Contact: Heidi Hilby, Washington Chapter, American College of Emergency Physicians, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

February 19—**(MONTANA) Laboratory/Clinical Management Rheumatologic Disorders.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

February 20-27—**(HAWAII) Cardiology.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

February 22—**Mt. St. Helens: Health Effects—Lung.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

February 24-26—**American College of Physicians: Clinical Topics in Pulmonary Disease.** Seattle. Wednesday-Friday. Virginia Mason Medical Center. Contact: VMMC.

February 26-27—**Stroke: Current Concepts.** Seattle. Thursday-Friday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education and Training Department, 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

February 26-28—**Cytology Continuing Education Workshop.** Seattle. Friday-Saturday. Northwest Hospital. Contact: CME Harborview.

February 27—**Behavioral Techniques in Primary Care.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Ed Oshiro, Office of Medical Education, Group Health Cooperative of Puget Sound, 200 15th Avenue East, Seattle, WA 98112. (206) 326-7348.

March 1-2—**(CALIFORNIA) Washington State Psychiatric Association: Treatment Issues in Geriatrics.** San Diego. Monday-Tuesday. Town and Country Hotel. Contact: Barbara Freda, Western Gerontological Society, 785 Market Street, Suite 1114, San Francisco, CA 94103. (415) 543-2617.

March 1-2—**Computers in Continuing Education.** Seattle. Monday-Tuesday. U/W Health Sciences Building. Contact: U/W.

March 4-5—**Gynecology for Primary MDs.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 5—**Adolescent Medicine.** Seattle. Friday. Child Development and Mental Retardation Center. Contact: U/W.

March 6—**Handicapped Child.** Seattle. Saturday. Child Development and Mental Retardation Center. Contact: U/W.

March 6-13—**(IDAHO)—Perinatal Critical Care.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

March 11-12—**Tacoma Academy of Internal Medicine—Annual Meeting.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 15—**(IDAHO) Site Visit.** Boise. Monday. Contact: U/W.

March 16—**Prevention/Treatment Thromboembolism.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

March 16—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

March 17—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

March 17—**Vasculitis.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

March 18—**(ALASKA) Stress Management With Children.** Anchorage. Thursday. Contact: U/W.

March 19—**Common Psychiatry Problems for Primary Care.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

March 19-20—**Common Psychiatry Problems for Primary Care Physicians.** Seattle. Friday-Saturday. U/W Health Sciences Bldg. Contact: U/W.

March 19-20—**Days of Pediatrics.** Tacoma. Friday-Saturday. Contact: CME Pierce County.

March 22—**Diagnosis and Management of Vasculitis.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

March 24—**(MONTANA) Recent Advances in Hematology.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

March 24—**(ALASKA) Cancer & Pregnancy.** Anchorage. Wednesday. Contact: U/W.

March 24-27—**(BRITISH COLUMBIA, CANADA) North Pacific Society of Neurology and Psychiatry.** Victoria, BC. Wednesday-Saturday. Empress Hotel. Contact: I. Blake Thompson, MD, 407-1120 Yates Street, Victoria, BC V8V-3M9, Canada.

March 25—**(MONTANA) Recent Advances in Hematology** Billings. Marillac Hall. Contact: U/W.

March 26—**(MONTANA) Recent Advances in Hematology** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

March 26-27—**Recombinant DNA and the Clinician.** Seattle Friday-Saturday. U/W South Campus Center. Contact: U/W

March 27-April 3—**(HAWAII) Obstetrics and Gynecology** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 27-April 3—**(HAWAII) Otolaryngology for Non-Otolaryngologists.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

March 29-April 9—**Rehabilitation Medicine Review.** Bellevue. Monday-Friday. Bellevue Hilton. Contact: U/W.

March 31—**Medicine and Civilization.** Seattle. Wednesday. U/W Health Sciences Building. Contact: U/W.

April 3-10—**(HAWAII) Topics in Family Practice.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 7, 14, 21, 28, May 5—**Medicine and Civilization.** Seattle. Wednesdays. U/W Health Sciences Building. Contact: U/W.

April 8—**Dermatology Conference.** Everett. Thursday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

April 9-10—**Management of Obesity: Scientific Approach.** Seattle. Friday-Saturday. Park Hilton. Contact: U/W.

April 10—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

April 10-17—**(HAWAII) Management of Pain.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 15-17—**Eleventh Annual Refresher Course in Diagnostic Radiology and Spinal CT Symposium.** Spokane. Thursday-Saturday. Sacred Heart Medical Center. Contact: Marvin J. Gottschall, MD, Director of Radiology, Sacred Heart Medical Center, TAF-C9, Spokane, WA 99220. (509) 455-3131.

April 15-17—**(MONTANA) Cytology Continuing Education Workshop.** Billings. Thursday-Saturday. Contact: CME Harborview.

April 17-24—**(HAWAII) Frontiers in Functional Neurosurgery.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 19—**(IDAHO) Early Cervical Cancer.** Boise. Monday. Contact: U/W.

April 20—**Detection/Rx Early Cervical Cancer.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

April 21—**Interstitial Lung Disease.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

April 21—**(MONTANA) What's New in Diabetes.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

April 22—**(MONTANA) What's New in Diabetes.** Billings. Thursday. Marillac Hall. Contact: U/W.

April 22-23—**Vascular Disease 1982: A Comprehensive Review for Primary Physicians.** Seattle. Thursday-Friday. South Campus Center. Contact: U/W.

April 23—**(MONTANA) What's New in Diabetes.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

April 26—**Urinary Infections New Developments in Nosocomial Infections.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

April 28—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

April 28-30—**Children's Orthopedic Hospital and Medical Center 75th Anniversary Pediatric Symposium.** Seattle. Wednesday-Friday. Children's Orthopedic Hospital and Medical Center. Contact: Donna Neumann, Medical Administration Office, Children's Orthopedic Hospital and Medical Center, P.O. Box 65371, Seattle, WA 98105. (206) 634-5377.

April 29—**Trauma.** Seattle. Thursday. Museum of History and Industry. Contact: U/W.

May 3—**Site Visit.** Omak. Monday. Contact: U/W.

May 3—**(ALASKA) Site Visit.** Ketchikan. Monday. Contact: U/W.

May 4—**(ALASKA) Site Visit.** Anchorage. Tuesday. Contact: U/W.

May 4—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

May 6-7—**(ALASKA) Cross Cultural Child Psychiatry.** Anchorage. Thursday-Friday. Contact: U/W.

May 7—**The Foot.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

May 13-15—**Third Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 14—**Medical Alumni.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

May 14-15—**Therapeutics in Common Medical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 19—**Breast Cancer & Acute Leukemia.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

May 20—**Estrogen Controversy.** Tacoma. Thursday. Contact: CME Pierce County.

May 21-22—**Topics in Emergency Room Medicine: The First 60 Minutes.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

May 24—**Fever Unknown Origin/Dx Elderly Dementia.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

May 26—**(ALASKA) Vaginitis.** Anchorage. Wednesday. Contact: U/W.

May 26—**(MONTANA) Health Problems of Physicians.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

May 26—**(MONTANA) Site Visit.** Kalispell. Wednesday. Contact: U/W.

May 27—**(MONTANA) Health Problems of Physicians.** Billings. Thursday. Marillac Hall. Contact: U/W.

May 27—**(MONTANA) Site Visit.** Whitefish. Thursday. Contact: U/W.

May 27-28—**Current Concepts in Management of Joint Disease.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

May 28—**(MONTANA) Health Problems of Physicians.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

May 29—**(IDAHO) Site Visit.** Pocatello. Saturday. Contact: U/W.

June 3-5—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

June 7—**(MONTANA) Site Visit.** Kalispell. Monday. Contact: U/W.

June 7—**(ALASKA) Site Visit.** Ketchikan. Monday. Contact: U/W.

June 8—**(ALASKA) Site Visit.** Anchorage. Tuesday. Contact: U/W.

June 8—**(MONTANA) Site Visit.** Whitefish. Tuesday. Contact: U/W.

June 11-12—**Common Minor Surgeries.** Seattle. Friday-Saturday. Park Hilton. Contact: U/W.

June 14—**(IDAHO) Vaginitis.** Boise. Monday. Contact: U/W.

June 14—**Site Visit.** Omak. Monday. Contact: U/W.

June 14-18—**Advances in Family Practice.** Seattle. Monday-Friday. U/W Health Sciences Building. Contact: U/W.

June 15—**Vaginitis.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

June 15—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

June 16—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

June 17-18—**(ALASKA) Behavior Medicine for GP's.** Anchorage. Thursday-Friday. Contact: U/W.

June 19-23—**(BRITISH COLUMBIA, CANADA) Canadian Congress of Laboratory Medicine & Pacific Northwest Society**

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: June 6-8, 1982, Chena Hot Springs.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. House of Delegates' Annual Meeting: May 28-29, 1982, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 12-17, 1982, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 21-24, 1982, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: 1982—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 28-31, 1982, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: 1982—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 14-16, 1982, MGM Grand Hotel, Reno.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 5-7, 1982, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: 1982—date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: 1982—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 7-10, 1982, Towne Motel, Yakima.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 30-July 3, 1982, Jackson Lake Lodge, Moran.

of Pathologists Meeting. Vancouver, BC. Saturday-Wednesday. Hotel Vancouver. Contact: G. R. Gray, MD, 201-660 West Seventh Avenue, Vancouver, BC V5Z IB5.

June 21-25—**Internal Medicine Review.** Seattle. Monday-Friday. Park Hilton. Contact: U/W.

June 23-27—**(OREGON) Ethics and History with Shakespeare.** Ashland. Wednesday-Sunday. Ashland Inn. Contact: U/W.

June 24-25—**EKG Interpretation and Arrythmias.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

June 24-26—**Medical Aspects of Dance.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact: U/W.

June 28—**Recent Advances in Hematology.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

July 23-25—**Washington State Society of Anesthesiologists: Seafair IV Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center. Contact: VMMC.

July 30-31—**Infertility.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

August 19-21—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

September 8-15—**13th International Cancer Congress.** Seattle. Wednesday-Wednesday. Seattle Center. Contact: Congress Operations Office, 13th International Cancer Congress, Fourth and Blanchard Building, Suite 1800, Seattle, WA 98121. (206) 621-9440.

September 16-18—**(WYOMING) Cytology Continuing Education Workshop.** Jackson. Thursday-Saturday. Contact: CME Harborview.

September 23-25—**Cytology Continuing Education Workshop.** Renton. Thursday-Saturday. Valley General Hospital. Contact: CME Harborview.

WYOMING

June 30-July 3—**Wyoming Medical Society Annual Meeting.** Moran. Wednesday-Saturday. Jackson Lake Lodge. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne. WY 82001. (307) 635-2424.

See Washington listing, September 16-18, 1982.

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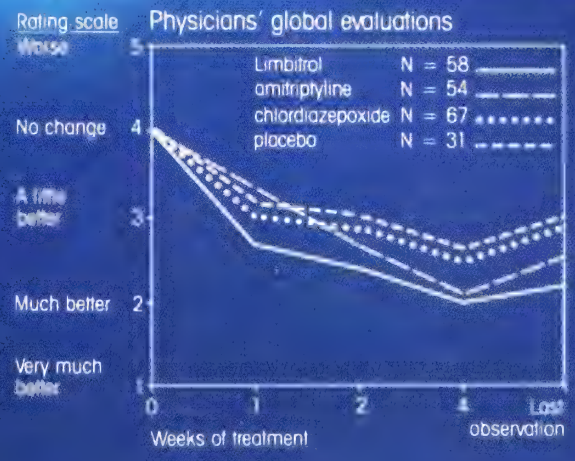

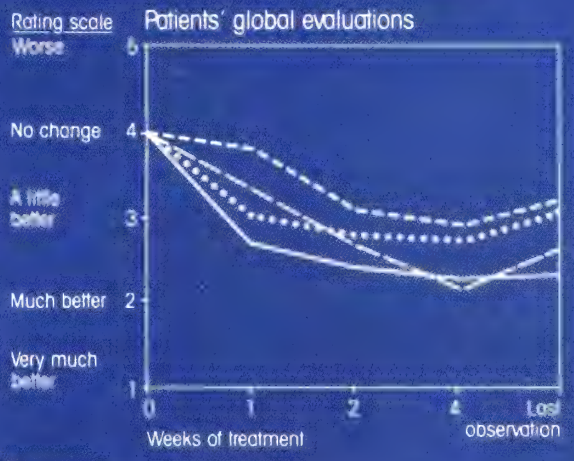

References:
1. Feighner JP, *et al: Psychopharmacology* 61:217-225, Mar 22, 1979
2. Data on file, Medical Department, Hoffmann-La Roche Inc

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Before prescribing, please consult complete product information, a summary of which follows:
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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving)

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Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide)
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated: sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects
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The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling
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Please see preceding page for a summary of product information.

THE WESTERN Journal of Medicine

VOLUME 136 • NUMBER 3 MARCH 1982

189 *Risk of Complications During Intravenous Heparin Therapy*
PRESTON H. NELSON, BS; KENNETH M. MOSER, MD; CAROL STONER, PharmD, and KATHLEEN S. MOSER, BS

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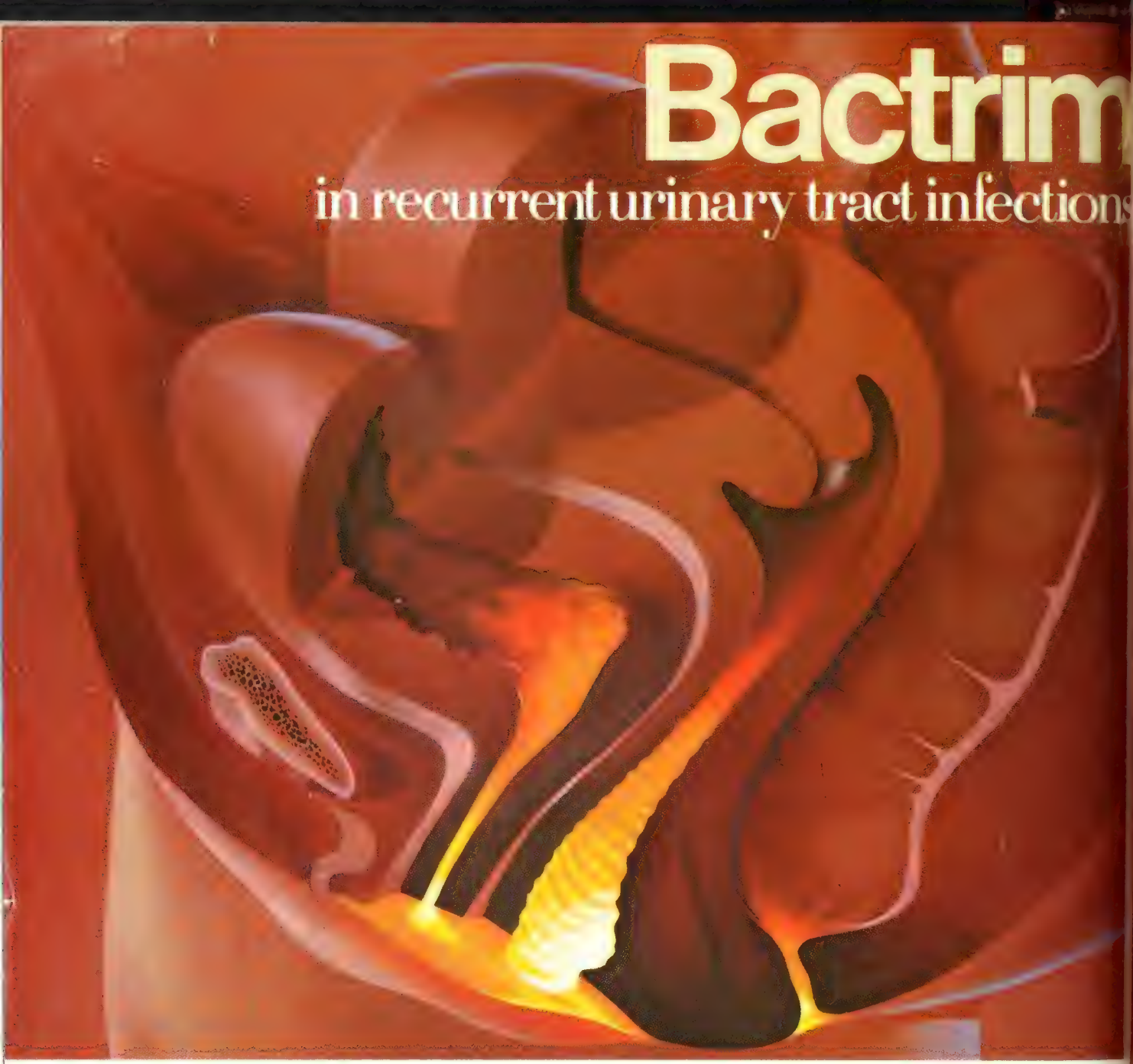

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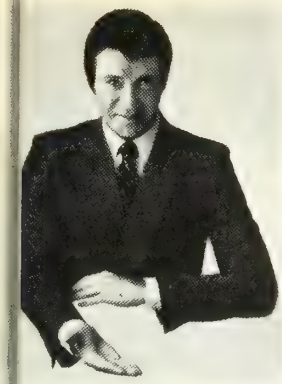

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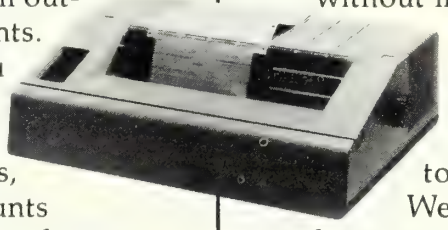

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From the Renal and Nuclear Medicine Services, Veterans Administration Medical Center, Palo Alto, California, and the School of Medicine, Stanford University, Stanford, California.

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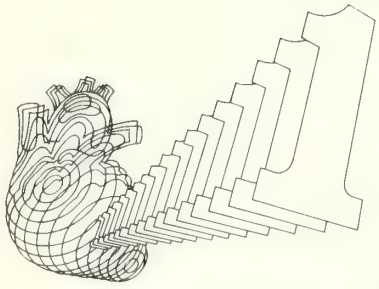

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DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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From the Division of Internal Medicine, LDS Hospital, and the Department of Internal Medicine, University of Utah College of Medicine, Salt Lake City.

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Dr. Patchen is Assistant Clinical Professor, Department of Obstetrics and Gynecology, University of Washington School of Medicine, and Associate Director, Breast Diagnostic Clinic, Seattle; and Dr. Schiller is Chairman of the Departments of Radiology, Waldo General Osteopathic Hospital and Shorewood Osteopathic Hospital, and Director of the Breast Diagnostic Clinic, Seattle, and Director of the Breast Diagnostic Clinic and Women's Diagnostic Clinic, Bellevue, Washington.

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From the Division of Clinical Chemistry, Vancouver General Hospital, and the Department of Medicine, University of British Columbia, Vancouver.

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It's LO/OVRAL 30. And here's how it holds spotting and breakthrough bleeding to a minimum: Hormone balance right from the start...and throughout the cycle. Hormone balance made possible with a very low dose oral contraceptive because of the supportive progestational activity of norgestrel, Wyeth's exclusive progestogen.

Regular withdrawal bleeding, too despite its low dose. In clinical trials amenorrhea—defined as absence of bleeding in the 7 pill-free days—was reported in only 2.1% of total cycles. And when defined as absence of bleeding for 60 days or more (as it often is), the incidence was only 0.2%.*

And comfort for most patients* thanks to the same balance that helps prevent spotting and breakthrough bleeding. In the clinical trials, most patients stayed free of common side effects such as nausea (0.6% of cycles), vomiting (0.1%), depression (0.5%) and acne (0.9%).

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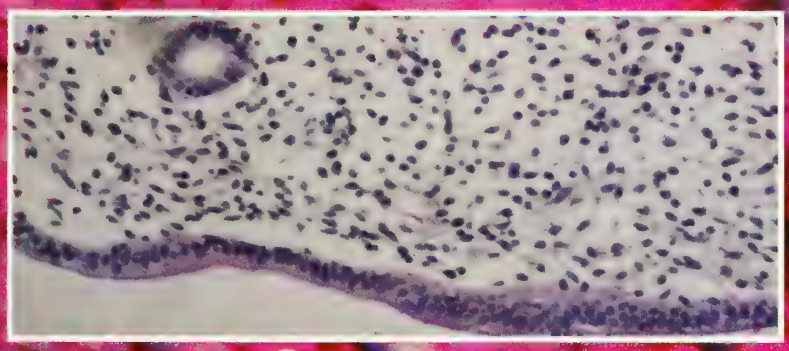

LO/OVRAL—1st cycle

Biopsy of intact endometrium in stable, progestogen suppressed state. Small, tubular gland in loose stroma without hemorrhage, fragmentation or debris characteristic of desquamating endometrium.

Even in the first cycle, the effective action of LO/OVRAL on the endometrium, such as you see here, provides the resistance against spotting and breakthrough bleeding you hope to achieve.

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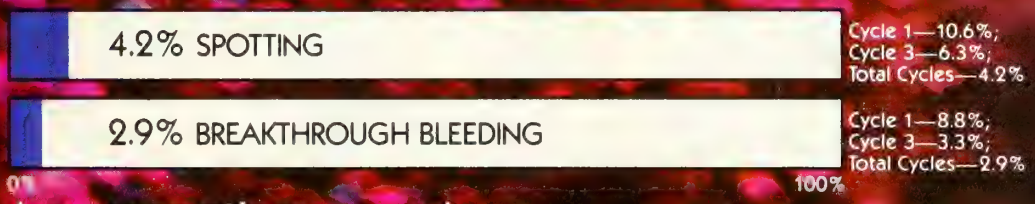

A near-spotless record— in clinical trials involving 22,489 cycles*

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. Contraindications, Warnings, Precautions, Adverse Reactions, etc., in the accompanying In Brief should be carefully considered.

See full prescribing information.

LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth

...with a near-spotless record!

See important information on following page.

IN BRIEF:

Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders. 3. Cerebral-vascular or coronary-artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified, quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000, ages 35-44—33/100,000, ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema, chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

LO/OVRAL® each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol

Wyeth Laboratories Phila., Pa. 19101

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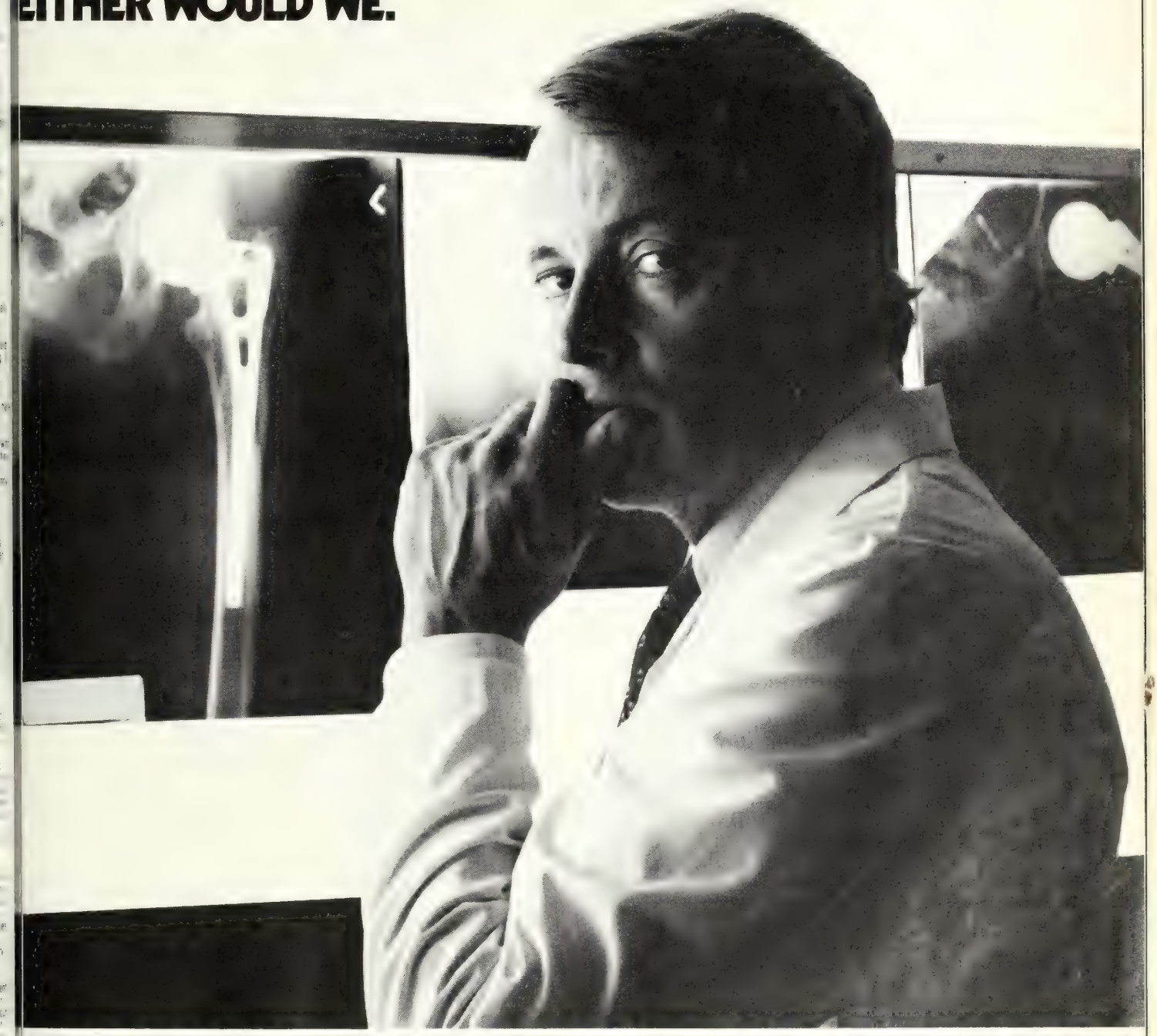

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ANESTHESIOLOGY

March 17-21—**American Society of Regional Anesthesia.** Del Monte Hyatt, Monterey. Wednesday-Sunday. 16 hrs. $175. Contact: Gale Thompson, MD, ASRA, P.O. Box 11083, Richmond, VA 23230. (804) 358-0305.

March 21-26—**Anesthesiology 1982—8th Annual Winter Meeting.** Anesthesiology Educational Foundation at Sierra Nevada Inn, Mammoth Lakes. Sunday-Friday. Contact: AEF, P.O. Box 24230, Los Angeles 90024.

April 3-10—**10th Obstetric Anesthesia Conference.** Dept. of Anesthesiology, Ohio State Univ. College of Medicine, at Sheraton Waikiki, Oahu, Hawaii. One week. 25 hrs. Contact: Dept. of Anesthesiology, c/o Bradford Travel, 1200 W. Henderson Rd., Columbus, OH 43220. (614) 457-9990 or (614) 421-8487 (OSU).

April 26-30—**6th Annual Hawaiian Seminar on Clinical Anesthesiology.** Calif. Society of Anesthesiologists at Maui Surf Hotel, Maui. Monday-Friday. 20 hrs. Contact: Educational Programs Div., CSA, 100 E. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

May 22-23—**Hemodynamic Monitoring/Pulmonary Artery Catheterization—Hands-on Workshops.** Calif. Soc. of Anesthesiologists and Stanford at Stanford. Saturday-Sunday. 15 hrs. $275, CSA members; $325, nonmembers. Contact: Educational Prog. Div., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

June 10-13—**California Society of Anesthesiologists—Annual Meeting.** Town and Country, San Diego. Thursday-Sunday. Contact: Educational Prog. Div., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

June 24-26—**Practical Closed Circuit Anesthesia II.** Pacific Medical Center at Hyatt at Union Square, San Francisco. Thursday-Saturday. 17 hrs. $300. Contact: Office of Cont. Ed., PMC, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

August 21-22—**Hemodynamic Monitoring/Pulmonary Artery Catheterization—Hands-on Workshops.** Calif. Soc. of Anesthesiologists and Stanford at Stanford. Saturday-Sunday. 15 hrs. $275, CSA members; $325, nonmembers. Contact: Educational Prog. Div., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

CANCER

March 25-27—**Western States Conference on Cancer Rehabilitation: Psychosocial, Physical and Economic Interventions.** No. Calif. Cancer Prog.; Am. Cancer Soc., Calif. Div.; UCLA Jonsson Comprehensive Cancer Ctr.; L.A. Co.-USC Comprehensive Cancer Ctr.; Community Cancer Control-L.A.; S.F. Regional Cancer Fndn. at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: Carrie Ewing, No. Calif. Cancer Prog., P.O. Box 10144, Palo Alto 94303. (415) 497-7431.

April 2-7—**Hematology/Oncology Update.** See Medicine, April 2-7.

April 3—**Oncology Update 1982.** Northridge Hospital Medical Center at Biltmore Hotel, Los Angeles. Saturday. 8 hrs. $125. Contact: Sandra Rozzen, Med. Ed. Dept., NHMC, 18300 Roscoe Blvd., Northridge 91328. (213) 885-5311.

April 15-17—**Cancer Symposium for Surgical and Medical Oncologists.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Saturday. 17 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 22-24—**Bladder Cancer.** American Urological Assn. at Biltmore Hotel, Los Angeles. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, AUA Office of Education, P.O. Box 25147, Houston, TX 77005.

(Continued on Page 53)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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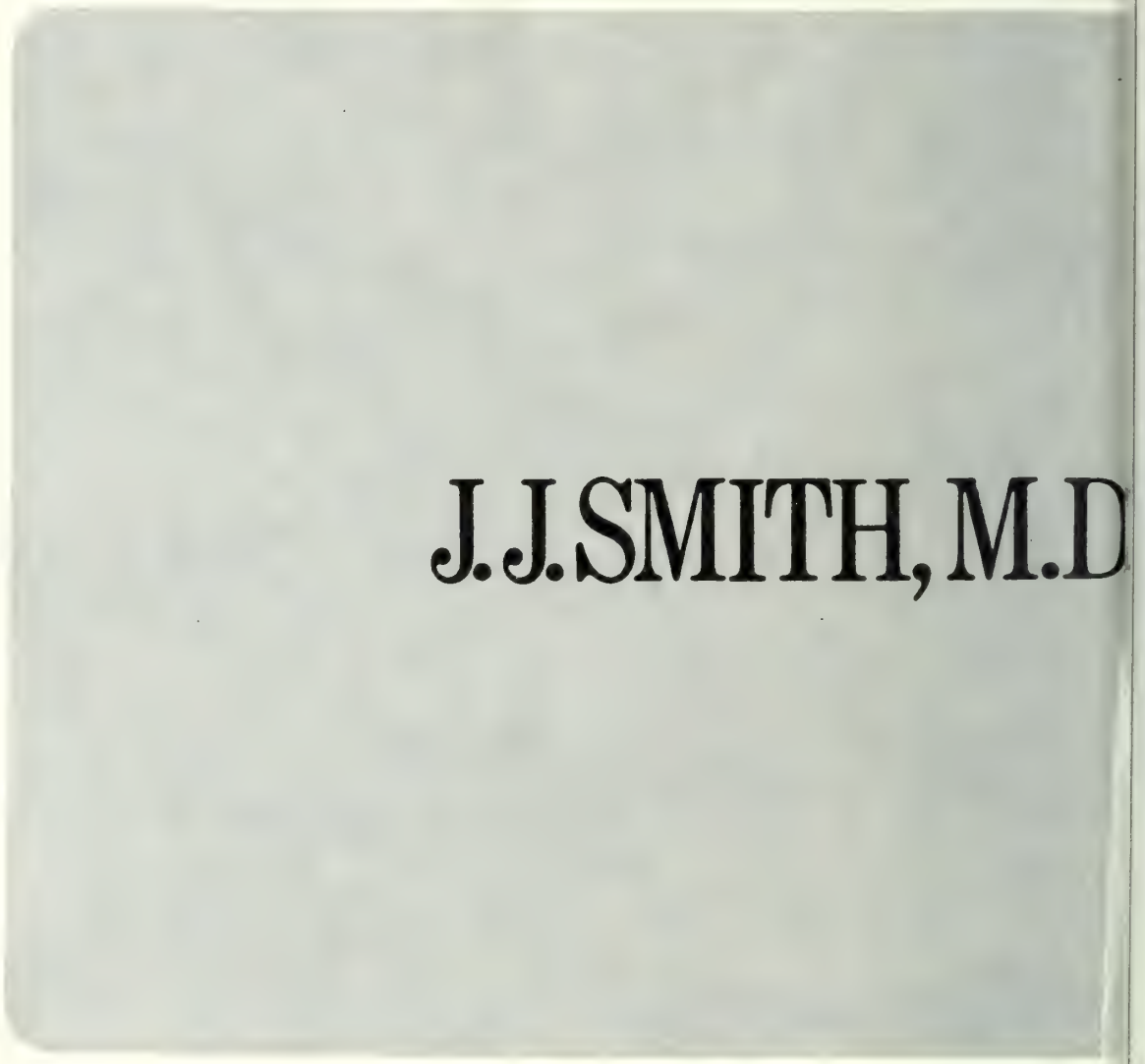

*For moderate to severe vasomotor symptoms, atrophic vaginitis, surgical menopause, postmenopausal osteoporosis†

PREMARIN® (CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

Counseling. It can help the menopausal woman through this difficult time. But counsel can't stop the moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard postmenopausal osteoporosis† the way PREMARIN tablets can.

PREMARIN. It may slow the progression of osteoporosis.† It controls her embarrassing sweats and hot flushes. Relieves her discomfo Helps her cope.** PREMARIN is a useful adjunct in your expert management of her menopausal symptoms.

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IT PREMARIN® HELPS HER CONDITION*

If her menopausal symptoms are limited to
rophic vaginitis, you're aware of the rapid,
tually complete relief PREMARIN Vaginal
eam provides. In the properly selected patient,
not only relieves the distressing symptoms of
trogen deficiency, such as dyspareunia,
yness and itching, but it rebuilds vaginal tissue.
PREMARIN Vaginal Cream. You know what it
n do.

ugated Estrogens Tablets have been evaluated as probably effective for postmenopausal
oporosis
e is no evidence that estrogens are effective for nervous symptoms or depression without
ciated vasomotor symptoms

ase see following page for Brief Summary of Prescribing Information.

PHYSICIANS WHO CARE.

for atrophic vaginitis

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM

0.625 mg/gm

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences - National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease
8. Prostatic carcinoma - palliative therapy of advanced disease
9. Postpartum breast engorgement - Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day, comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. With doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain, tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormally excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test

g. Reduced serum folate concentration

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption, loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer - 1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women - 10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. 872 - Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available - Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. 7814/284

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

In an era of change,
An Agent of Change...

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- A distinct same

Brief Summary

Indications an relief of sympto Anxiety or tens require treatme Effectiveness assessed by sy the drug for the

Contraindicati angle glaucoma

Warnings: Not As with all CNS- vehicles, and of Physical and noted with barb tinuance of ben muscle cramps drug addicts an benzodiazepine dence. Withdra continuance of several months

Precautions: I suicide. For elderly or 2mg to avoid o drawal of any treated: anxiety vulsions. Obser Where gastroin that lorazepam testinal or card treated with lor was 1.25mg/kg 10mg/day). Effe months of first lorazepam for quent monitorir ness in children ESSENTIAL LA penia; some ha periodic blood term therapy.

CLINICALLY SI duce CNS depr barbiturates or

CARCINOGEN potential emerg mutagenesis ha

Your patients are changing

...the population is getting older, more people are holding a second job, patients are more concerned about the medications they take.

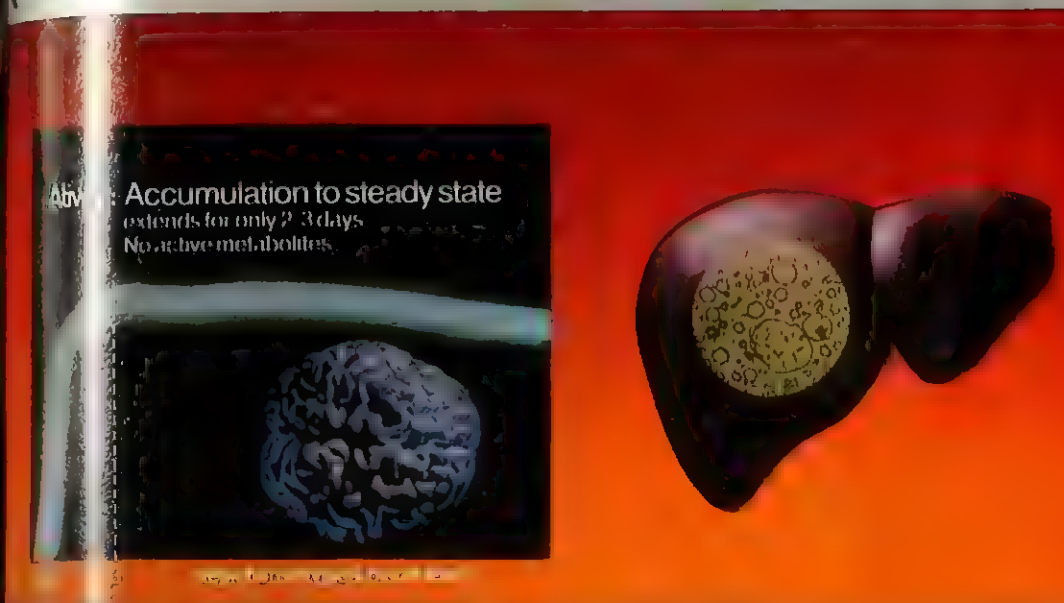
Medical knowledge is changing

...there are diagnostic resources and surgical techniques undreamed of only a few years ago, biomedical engineering, new insights also into the action of drugs.

In this changing environment, the way you are practicing medicine is changing too...

Twenty years ago, the benzodiazepines represented a real step forward in the management of anxiety and tension states. In recent years, however, concern about drug accumulation and clearance has led physicians to re-evaluate their use of these agents. In light of current knowledge, many clinicians are changing from multi-metabolite benzodiazepines to Ativan® (lorazepam)—a metabolically and pharmacokinetically distinctive agent that offers clinical advantages which more closely meet the expectations of a modern anxiolytic.

Ativan®: Agent of Change
(lorazepam)



because...

it's shorter acting, with less accumulation*

In contrast to long-acting benzodiazepines, Ativan has a short, 12-hour half-life, and no active metabolites. In multiple-dose therapy, Ativan accumulates for only two to three days before reaching steady state; the long-acting benzodiazepines—diazepam CIV, chlordiazepoxide CIV, clorazepate CIV and prazepam CIV—with their active metabolites—accumulate for as long as 20 days, increasing the likelihood of excessive sedation.

it doesn't interact with drugs metabolized by P450 microsomal enzymes

Most benzodiazepines undergo oxidative metabolism and thus utilize the hepatic microsomal enzyme system. Ativan® (lorazepam), however, is metabolized by glucuronidation and does not compete with other drugs for cytochrome P450. Thus, when Ativan is given with Tagamet® (cimetidine), for example, clearance is not delayed, nor sedation increased†—unlike reported observations with patients on other benzodiazepines.[1-5]

it gives you greater control of therapy

The short half-life of Ativan® facilitates more rapid response to dosage adjustments, allowing you to titrate therapy to patients' changing needs. Also, once you decide to discontinue Ativan, it will be out of your patient's system four days after the final dose—in contrast to long-acting benzodiazepines and their active metabolites which take as long as two weeks to be totally eliminated.

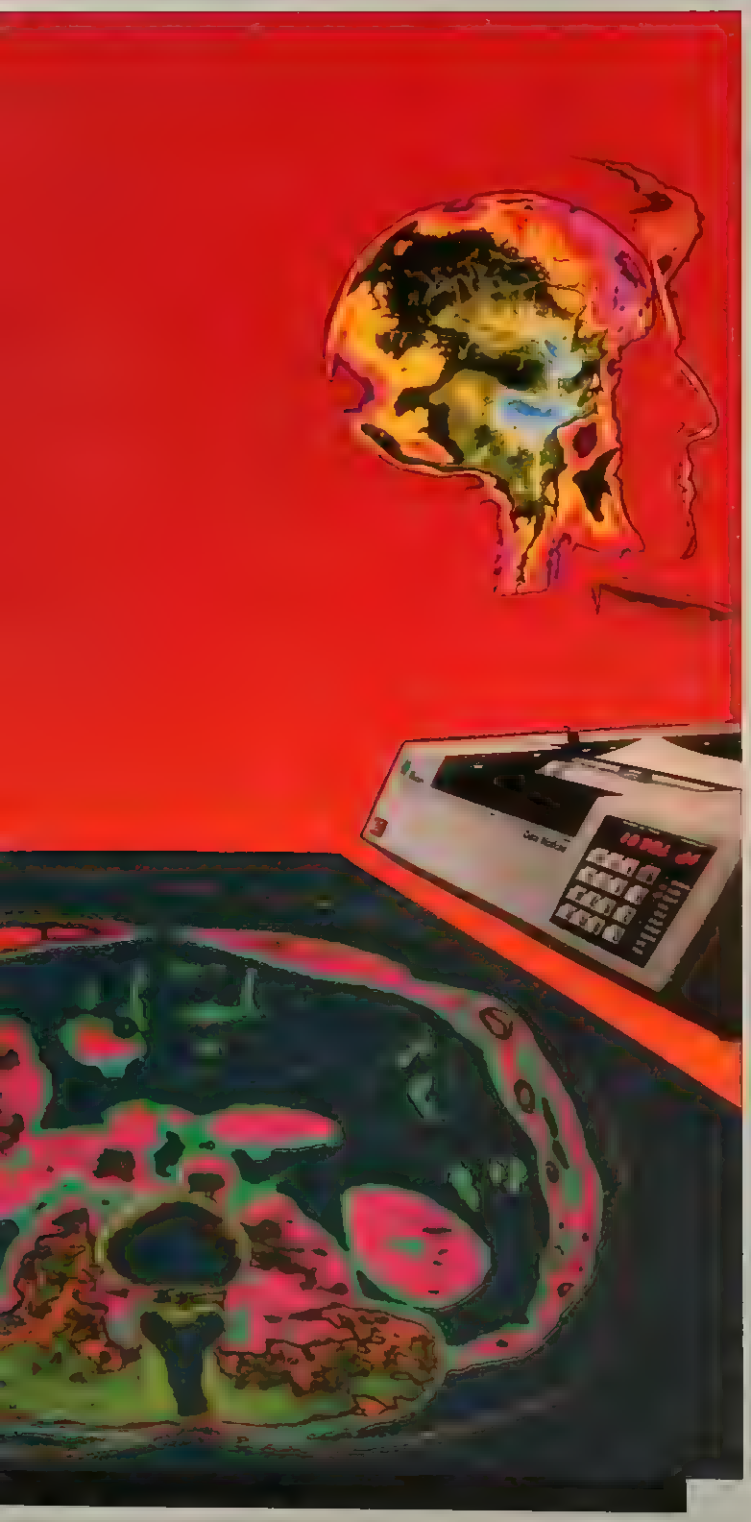
Ativan®
for (lorazepam) IV
Anxiety

See important information on following page.

1. Klotz U, Reimann I: N Engl J Med *302*:1012-1014, 1980
2. Desmond PV, Patwardhan RV, Schenker S, et al: Ann Intern Med *93*:266-268, 1980.
3. Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology *79*:912-916, 1980
4. Jeavers EM, Naranjo CA, Peachey JE: N Engl J Med *305*:1255-1262, 1981
5. Ruffalo RL, Thompson JF, Segal JL: South Med J *74*:1075-1078, 1981

*Pharmacokinetics cannot as yet be directly related to efficacy

†All benzodiazepines produce additive effects when given with CNS depressants such as barbiturates or alcohol



Ativan®: Agent of Change
(lorazepam) ℞

- Little accumulation lessens likelihood of excessive sedation
- Unlike most benzodiazepines, Ativan does not compete with other drugs, such as Tagamet® (cimetidine), for microsomal enzyme system during biotransformation
- Metabolism not affected by age or liver dysfunction
- Short half-life provides greater control of therapy
- Promptly eliminated from patient's system after discontinuation
- Specifically evaluated and found effective for anxiety associated with cardiovascular and gastrointestinal disorders
- A distinctive change from long-acting benzodiazepines, all of which have active metabolites and are much the same

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps) vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months

Precautions: In depression accompanying anxiety, consider possibility for suicide

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed

PREGNANCY: Reproductive studies were performed in mice, rats, and strains of rabbits. Occasional anomalies (reduction of tarsals tibia, fe sals, malrotated limbs, gastroschisis, malformed skull and microphth were seen in drug-treated rabbits without relationship to dosage. Altho these anomalies were not present in the concurrent control group, they been reported to occur randomly in historical controls. At 40mg/k higher, there was evidence of fetal resorption and increased fetal loss bits which was not seen at lower doses. Clinical significance of these is not known. However, increased risk of congenital malformat ons assoc with use of minor tranquilizers (chlordiazepoxide, diazepam and mepr mate) during first trimester of pregnancy has been suggested several ies. Because use of these drugs is rarely a matter of gency, lorazepam during this period should almost always be avoide Possibly a woman of child-bearing potential may be pregnant at insti on of th should be considered. Advise patients if they become pregn t to comm cate with their physician about desirability of discontinu the dru humans, blood levels from umbilical cord blood indicate plac tal transf lorazepam and its glucuronide

NURSING MOTHERS: It is not known if oral lorazepam is ex ted in hu milk like other benzodiazepines. As a general rule, nursin hould n undertaken while on a drug since many drugs are excreted in k

Adverse Reactions, if they occur, are usually observed beginni therapy and generally disappear on continued medication c n decre dose. In a sample of about 3,500 anxious patients, most f uent adv reaction is sedation (15.9%), followed by dizziness (6.9%), w kness (4 and unsteadiness (3.4%). Less frequent are disorientation, d ression, sea, change in appetite, headache, sleep disturbance, agitat dermatit cal symptoms, eye function disturbance, various gastrointes a sympt and autonomic manifestations. Incidence of sedation an nstead increased with age. Small decreases in blood pressure have en noted are not clinically significant, probably being related to relief of xiety

Overdosage: In management of overdosage with any drug, bear in multiple agents may have been taken. Manifestations of over sage inc somnolence, confusion and coma. Induce vomiting and/or ur rtake ga lavage followed by general supportive care, monitoring vital ns and observation. Hypotension, though unlikely, usually may be ntrolled Levarterenol Bitartrate Injection U.S.P. Usefulness of dialys as not determined

Dosage: **Individualize for maximum beneficial effe s. Incre dose gradually when needed, giving higher evening dose b increasing daytime doses. Anxiety, usually 2-3mg/day ven b.i.d. t.i.d.; dosage may vary from 1 to 10mg/day in divide doses elderly or debilitated, initially 1-2mg/day; insomnia due to anxie transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories Philadelphia, PA 19101

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Motrin®
ibuprofen, Upjohn
600 mg Tablets

More convenient for your patients

Upjohn

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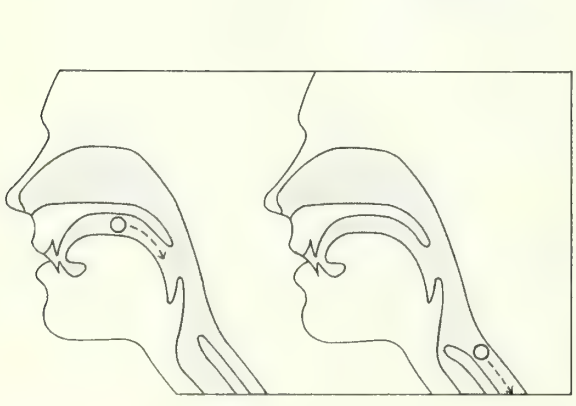
J4043-4 July 1981

If you've never recommended a specific brand of aspirin before,

now's the time to start!

Better tolerated than regular aspirin



Now, by means of a unique water-soluble cellulose coating, Improved Bayer® Aspirin provides oro-pharyngo-esophageal protection for your patients. Furthermore, in a recent short term use study, perceived stomach upset was shown to be no greater than seen with placebo.[1]

This patented coating is *not* enteric in nature, so it is not affected by pH. And the film does not affect absorption or bioavailability. What it does is to stay intact just long enough for tablets to reach the stomach. Disintegration in the buccal cavity, pharynx and esophagus is avoided—easing swallowing and minimizing aspirin

taste, aftertaste and burning in the throat. Once tablets reach the stomach, they dissolve quickly and completely—producing the same aspirin and salicylate blood levels as regular aspirin.[2]

Protective effect demonstrated in multi-center study[1]

In a double-blind, multi-center clinical study,[1] involving 907 subjects, Improved Bayer Aspirin was shown significantly superior to regular aspirin in avoiding aspirin taste, aftertaste, dissolution of tablets in the mouth and burning in the throat.

As well tolerated as placebo

What's more, for short term use when compared to both coated and uncoated placebo tablets, Improved Bayer Aspirin showed *no significant difference in subjective complaints of stomach upset*-as shown in the chart:

Subjective evaluations—average percentage of complaints following each of three 650 mg doses of Improved Bayer Aspirin, placebo and coated placebo—given four hours apart[1]

Symptom & Time of Administration*	Improved Bayer Aspirin	Placebo	Coated Placebo
Burning in Throat			
5 min.	6%	5%	5%
20 min.	8%	7%	8%
50 min.	6%	5%	5%
Stomach Upset			
5 min.	2%	4%	2%
20 min.	6%	8%	5%
50 min.	8%	7%	5%
Nausea			
5 min.	0%	1%	0%
20 min.	2%	3%	2%
50 min.	3%	2%	2%

* Following each of the three doses of test formulations, subjective side effects were recorded at 5, 20 and 50 minutes.

Better patient compliance

With its low incidence of subjective complaints and high degree of acceptance, Improved Bayer Aspirin can help assure the kind of patient compliance needed for successful salicylate therapy.

Now, more than ever—Bayer is the name to specify

To be sure your patients get all the benefits of Improved Bayer Aspirin, be sure to specify the name Bayer, whenever you recommend aspirin. Now, more than ever, it can make an important difference.

References:
1. Soller, R. W. and Baretz, D.B.: Methylcellulose Film Coating of Tablets as an Improved Delivery System for Aspirin (to be published).
2. Soller, R. W.: Bioavailability of Improved Bayer Aspirin (on file, The Bayer Company).

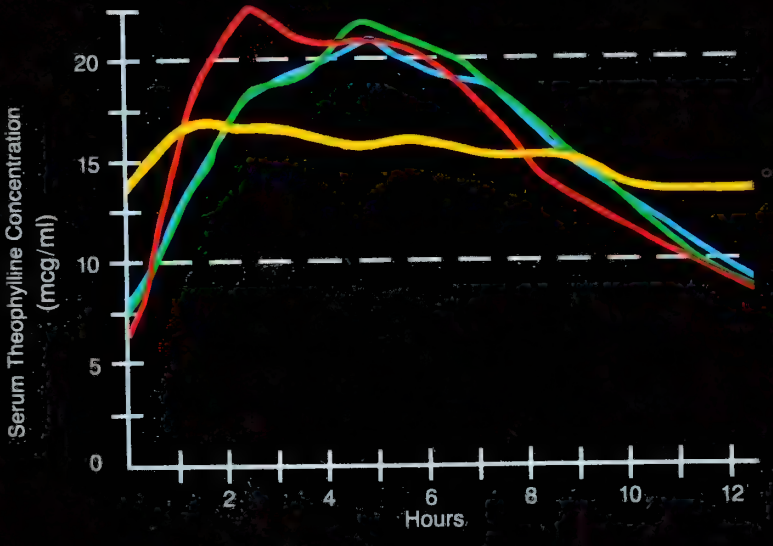
The Bayer Company
Glenbrook Laboratories
A Division of Sterling Drug Inc.
90 Park Avenue
New York, New York 10016

Introducing Improved BAYER® ASPIRIN

Projected steady-state levels:
THEO-DUR®
(anhydrous theophylline)

VS.

Other forms of
sustained-release theophylline:†



- THEO-DUR®
- LāBID™
- Theolair™-SR/Respbid™
- Slo-Phyllin® Gyrocaps®

The lines are drawn.

THEO-DUR® (anhydrous theophylline) –The first and only form of oral theophylline to demonstrate linear blood levels for a full 12 hours in virtually all patients, even those who are rapid metabolizers.

Until THEO-DUR, blood levels from rapid acting and sustained action theophyllines generally showed unacceptably wide peak-trough fluctuations. This meant the drug was difficult to maintain in the therapeutic range and difficult to sustain in that range for more than a few hours.

For most patients, the therapeutic range of theophylline falls somewhere between 10 and 20 mcg/ml. When serum concentrations fall much below 10, they are often ineffective. When they go much above 20, they are usually toxic.

Now, with THEO-DUR, you can provide your patient with maximum theophylline protection and avoid theophylline failure.

And, since THEO-DUR can maintain therapeutic blood levels for a full 12 hours, patients can enjoy a full day of normal activities and a night of uninterrupted sleep.

Zero-order THEO-DUR–a unique form of oral theophylline.

THEO-DUR provides zero-order drug absorption. The theophylline is absorbed into the blood at an essentially constant quantity per hour.

Other oral forms of theophylline have first-order absorption, in which the largest amount is absorbed in the first hour and proportionately smaller amounts thereafter.

When absorption varies, as it does with first-order drugs, protection can also vary. That's why first-order theophyllines can be toxic within the first few hours and subtherapeutic later on.

THEO-DUR–the practical benefits.

Your patient benefits from the maximum control provided by THEO-DUR in several important ways: exercise tolerance is increased, emergency hospital visits are less likely and concomitant therapy is usually unnecessary.

Dosage titration is easy to achieve.* THEO-DUR is the only sustained action tablet in 200 mg as well as 100 and 300 mg strengths and all tablets are scored for greater dosage flexibility.

THEO-DUR also enhances patient compliance–with an every 12-hour dosage schedule that's easier to remember.

**After three days, on a steady dose, serum concentrations should be monitored and appropriate dosage adjustments made, if necessary.*

†*Adapted from Weinberger* et al: J Pediatr 99 *(no. 1): 145, July, 1981. Serum concentrations computer-projected from single dose absorption data in normal subjects supplied by the manufacturer or obtained experimentally (available on written request). Based on a rapid theophylline half-life of 3.7 hours, after achievement of steady-state levels with curves normalized to a concentration of 15 mcg/ml.*

Today's most widely prescribed bronchodilator.

THEO-DUR®

(anhydrous theophylline)

Sustained Action Tablets

KEY PHARMACEUTICALS, INC.

Please see next page for a summary of prescribing information.

THEO-DUR®

(anhydrous theophylline)
Sustained Action Tablets

Today's most widely prescribed bronchodilator.

Description: THEO-DUR Sustained Action Tablets contain anhydrous theophylline, with no color additives
Pharmacologic Actions: The pharmacologic actions of theophylline are as a bronchodilator, pulmonary vasodilator and smooth muscle relaxant since the drug directly relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels. Theophylline also possesses other actions typical of the xanthine derivatives: coronary vasodilator, diuretic, cardiac stimulant, cerebral stimulant and skeletal muscle stimulant. The actions of theophylline may be mediated through inhibition of phosphodiesterase and a resultant increase in intracellular cyclic AMP which could mediate smooth muscle relaxation
Indications and Usage: Symptomatic relief and/or prevention of asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.
Contraindications: THEO-DUR is contraindicated in individuals who have shown hypersensitivity to any of its components or xanthine derivatives
Warnings: Excessive theophylline doses may be associated with toxicity; serum theophylline levels should be monitored to assure maximum benefit with minimum risk. Incidence of toxicity increases at serum levels greater than 20 mcg/ml. High blood levels of theophylline resulting from conventional doses are correlated with clinical manifestation of toxicity in: patients with lowered body plasma clearances, patients with liver dysfunction or chronic obstructive lung disease, and patients who are older than 55 years of age, particularly males. There are often no early signs of less serious theophylline toxicity such as nausea and restlessness, which may appear in up to 50% of patients prior to onset of convulsions. Ventricular arrhythmias or seizures may be the first signs of toxicity. Many patients who have higher theophylline serum levels exhibit a tachycardia. Theophylline products may worsen pre-existing arrhythmias.
Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established. This is, unfortunately, true for most anti-asthmatic medications. Therefore, use of theophylline in pregnant women should be balanced against the risk of uncontrolled asthma
Precautions: THEO-DUR TABLETS SHOULD NOT BE CHEWED OR CRUSHED. Theophyllines should not be administered concurrently with other xanthine medications. It should be used with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, and in the elderly, particularly males, and in neonates. Great caution should be used in giving theophylline to patients in congestive heart failure since these patients show markedly prolonged theophylline blood level curves. Use theophylline cautiously in patients with history of peptic ulcer. Theophylline may occasionally act as a local irritant to G.I. tract, although gastrointestinal symptoms are more commonly central and associated with high serum concentrations above 20 mcg/ml.
Adverse Reactions: The most consistent adverse reactions are usually due to overdose and are
Gastrointestinal: Nausea, vomiting, epigastric pain, hematemesis, diarrhea.
Central Nervous System: Headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.
Cardiovascular: Palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, life threatening ventricular arrhythmias
Respiratory: Tachypnea.
Renal: Albuminuria, increased excretion of renal tubular cells and red blood cells, potentiation of diuresis
Others: Hyperglycemia and inappropriate ADH syndrome
How Supplied: THEO-DUR 100 mg, 200 mg and 300 mg Sustained Action Tablets are available in bottles of 100, 500, 1000, and 5000, and in unit dose packages of 100
Caution: FEDERAL LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION
For full prescribing information, see package insert.
0881

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Miami, Florida 33169 (USA)

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Physicians – Stress & Coping 1982

Weekend Workshops for Physicians and Spouses

During this weekend, physicians and spouses, together with faculty, will examine sources of stress, stress reduction strategies and concerns unique to physicians and their family members.

April 2-4, Aliso Creek Inn, South Laguna
April 23-25, The Inn, Rancho Santa Fe
April 30-May 2, El Encanto, Santa Barbara
May 14-16, Stanford Sierra Lodge, South Lake Tahoe
May 28-30, Asilomar, Pacific Grove
August 27-29, La Playa Hotel, Carmel
September 10-12, Sea Lodge, La Jolla
October 8-10, Half Moon Bay Lodge Half Moon Bay

For each weekend, there is a registration fee and a separate fee for room and board.
Registration is $190 per couple or $120 per person.

For information and to register, contact California Medical Association, Committee on the Well-Being of Physicians, 731 Market Street, San Francisco, CA 94103. Call (415) 777-2000, Ext. 138

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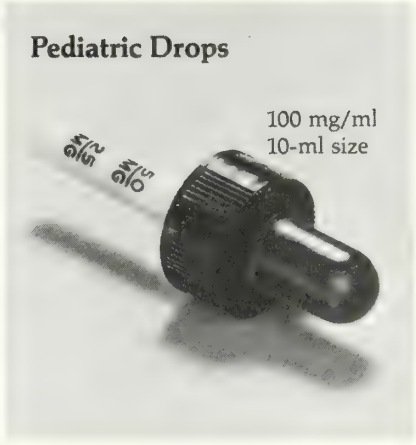

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Something
happens...

Depressive,
anxiety
AND
somatic
symptoms respond
rapidly...

without a phenothiazine

A special quality of relief typically comes early to anxious depressed patients treated with Limbitrol. For example, core depressive symptoms—feelings of guilt and worthlessness—often respond within a week. So do insomnia, anorexia, agitation, and psychic and somatic anxiety. And as the anxious depression responds, so, often do the related somatic symptoms—headache, backache, G.I. upset, palpitations.* No less important to the patient's progress is the enhanced compliance that comes with the early sense of well-being.

With Limbitrol, these striking results are obtained without the phenothiazines contained in other dual medications. The causal relationship between the phenothiazines and extrapyramidal side effects, including tardive dyskinesia, is well established. In contrast, the reported incidence of these adverse reactions with Limbitrol or either of its components is rare.

Patients should be cautioned about the combined effects with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car.

*Data on file, Medical Department, Hoffmann-La Roche Inc.

Please see summary of product information on following page.

in moderate depression and anxiety

Limbitrol® 5-12.5 10-25

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

A special quality of relief

ROCHE®

LIMBITROL® TABLETS Tranquilizer–Antidepressant
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Relief of moderate to severe depression associated with moderate to severe anxiety
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction
Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).
***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide)
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated: sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12.
In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
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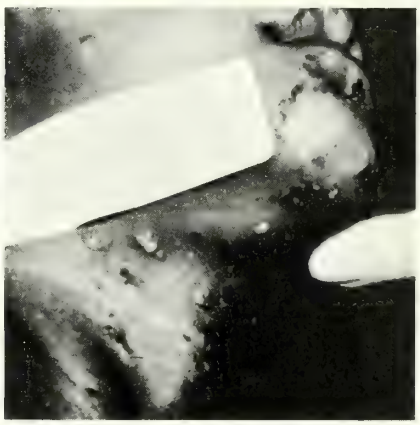

After one week of penicillin V-K therapy

Two weeks after initiation of TEGOPEN therapy

Treatment failure was judged to have occurred when lesions increased in size and/or number during the initial week of treatment with penicillin V-K. *No* treatment failures occurred with Tegopen.

*Data on file, Bristol Laboratories.

Brief Summary of Prescribing Information

TEGOPEN®
(cloxacillin sodium)
Capsules and Oral Solution

For complete information, consult Official Package Circular. (12) 9/11/75

INDICATIONS:

Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed.

IMPORTANT NOTE

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

CONTRAINDICATIONS:

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

RESULTS OF ORAL THERAPY revealed a high percentage of treatment failures with penicillin V potassium, but *no* failures with Tegopen.

		Given Tegopen® (*cloxacillin sodium*)	Given *penicillin V-K*
Staphylococcus aureus	(78 patients)	39	39
Returned to clinic at one week		29†	38†
Treatment failure at one week		0	18 (47.4%)
Staphylococcus aureus* and *Streptococcus pyogenes	(9 patients)	4	5
Returned to clinic at one week		4	5
Treatment failure at one week		0	2 (40%)
No initial bacterial growth	(14 patients)	9	5
All 14 healed, regardless of which antibiotic was administered.			
Beta-hemolytic *Streptococcus*	(1 patient)	0	1
TOTALS:	**102 patients**	**52 patients**	**50 patients**

†Eleven patients did not return for their one-week checkup These were all called by telephone, and their families reported the lesions had healed. One patient was dropped from the study, early, because of adverse reaction to medication

STUDY: DESCRIPTION/PROTOCOL

- 102 nonselected subjects, with initial bacteriology as follows: 77% *Staphylococcus aureus,* 9% mixed *Staphylococcus aureus* and *Streptococcus pyogenes,* and 1% beta-hemolytic *Streptococcus*.‡
- All patients were given randomized therapy—Tegopen capsules or oral solution, or penicillin V-K tablets or oral solution, in recommended dosages according to body weight.
- All patients were evaluated after one week's therapy. If there was no improvement, therapy was switched to the other antibiotic. The "other antibiotic" proved to be Tegopen 100% of the time because no treatment failures had occurred with Tegopen.
- A final assessment of progress was made two weeks after initiation of Tegopen therapy.

‡The remainder, to equal 100%, consisted of 14 patients (13%) who exhibited no initial bacterial growth. These 14 were all healed, whether given Tegopen or penicillin V-K

TEGOPEN®
(cloxacillin sodium)
–effective therapy for staph infections of the skin and skin structures

WARNING:
Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids

Safety for use in pregnancy has not been established

PRECAUTIONS:
The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy

ADVERSE REACTIONS:
Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

USUAL DOSAGE:
Adults: 250 mg. q.6h

Children: 50 mg./Kg./day in equally divided doses q.6h. Children weighing more than 20 Kg. should be given the adult dose. Administer on empty stomach for maximum absorption.

N.B. INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS

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Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K+ supplement or K+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K+ supplement or K+-sparing agent).

Serum K+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction hyperkalemia. Pre-existing elevated serum potassium Hypersensitivity to either component or other sulfonamide-derived drugs

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Watch for signs of impending coma in severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia have been reported with thiazides. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function

Thiazides may add to or potentiate the action of other antihypertensive drugs

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide' although a causal relationship has not been established

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); In Patient-Pak™ unit-of-use bottles of 100.

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THE WESTERN
Journal of Medicine

Refer to: Nelson PH, Moser KM, Stoner C, et al: Risk of complications during intravenous heparin therapy. West J Med 136:189-197, Mar 1982

Risk of Complications During Intravenous Heparin Therapy

PRESTON H. NELSON, BS; KENNETH M. MOSER, MD; CAROL STONER, PharmD, *and* KATHLEEN S. MOSER, BS, *San Diego*

The records of all patients to whom heparin was dispensed by the pharmacy of the University of California Medical Center, San Diego, during the year 1979 were reviewed. A total of 131 patients above age 15 met the inclusion criteria —they had received more than 10,000 units of heparin per 24 hours for at least 24 hours. All 131 patients were administered heparin by continuous intravenous infusion by peristaltic pump. All heparin was porcine heparin from a single commercial source. The daily mean minimum dose averaged 19,700 units, the maximum, 25,600 units. The activated partial thromboplastin time, usually measured once a day, was the only test used to monitor the dose. Major complicating events occurred in 13 patients (10 percent), and minor complicating events occurred in 10 patients (7.6 percent). All major complicating events occurred in patients with serious concurrent diseases. In subpopulations of 58 patients without concurrent disease, and of 24 in whom heparin was initiated for suspicion of thromboembolism that was not confirmed, no major complicating events occurred. These data indicate that continuous, intravenous administration of heparin is associated with minimal risk, and that risk is concentrated among older patients with serious concurrent disease.

THERE IS CONSENSUS that heparin is the drug of choice in the treatment of venous thromboembolism, except in patients in whom thrombolytic agents may be considered as initial therapy.[1-3] However, there is no consensus about the extent of diagnostic information required before heparin therapy is initiated,[4-7] the optimal-dose regimen or the most appropriate approach to monitoring for safety and efficacy.[7-16]

Two major factors contribute to these ongoing controversies. One is the variety of invasive and noninvasive approaches available for the diagnosis of deep venous thrombosis and pulmonary embolism;[4-7] the other is the perception of the risk of hemorrhage associated with heparin therapy. The two are related because the perception of risk

From the Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California Medical Center, San Diego.

Supported in part by the Thrombosis Program Project (HL-18576) of UCSD and the National Heart, Lung and Blood Institute.

Submitted, revised, October 19, 1981.

Reprint requests to: Kenneth M. Moser, MD, Professor of Medicine, University Hospital, 225 Dickinson Street, San Diego, CA 92103.

ABBREVIATIONS USED IN TEXT

APTT = activated partial thromboplastin time
BUN = blood urea nitrogen
CVA = cerebrovascular accident
DVT = deep venous thrombosis
PE = pulmonary embolism

determines the extent of the data base on which the decisions to initiate and maintain heparin therapy are made.

To gain insight into the ways in which heparin is used and monitored and into the risks associated with its use, we reviewed the records of all patients who received heparin at the University of California Medical Center, San Diego, during a full calendar year (1979). There is no *anticoagulant team* that dictates the heparin regimen at this medical center; the regimen is selected by the attending physicians and house staff on individual hospital ward services. Therefore, we felt such a review would provide insight into the actual practice and experience with heparin—without the constraints mandated by a protocol.

Patients and Methods

At the Medical Center, the pharmacy dispenses all heparin used. Using these pharmacy records, we identified all patients who received heparin during the period January 1, 1979, through December 31, 1979. Within this group we selected all patients 15 years of age or older who received heparin intravenously in a dose of at least 10,000 units per day for at least 24 hours. All heparin used during this period was from porcine intestinal mucosa from a single commercial source (Organon, West Orange, NJ).

The following data were obtained from the records of each patient: age; sex; service to which the patient was admitted; indication for heparin therapy; other diagnoses; method of heparin administration; laboratory tests used to monitor heparin therapy; duration of heparin administration and daily dose; history of abnormal bleeding or peptic ulcer disease; history of trauma or surgical or invasive procedure (excluding simple venipuncture and arterial puncture) within ten days before initiation of heparin; intramuscular injections or concurrent treatment with drugs having possible anticoagulant effects; any hemorrhagic event, transfusion, wound hematoma or thrombocytopenia coincident with heparin administration; hematocrit and hemoglobin values during heparin administration, and the eventual outcome of each patient's course in hospital. The following data were obtained when available: activated partial thromboplastin time (APTT), platelet count, blood urea nitrogen (BUN) and serum creatinine levels before and during heparin therapy. Autopsy reports were reviewed for all patients who died during hospital stay.

TABLE 1.—*Distribution of Heparin-Treated Patients by Indications for Heparin Therapy and Sex*

Indication	*Males*	*Females*
Presumed deep venous thrombosis (DVT)	24	18
Presumed pulmonary embolism (PE)*	28	17
Following arterial operation	27	2
Others†	8	7
TOTAL	87	44

*Patients with both DVT and PE were recorded as PE.

†Status postcerebrovascular accident (CVA), 4; arterial embolization, 3; diffuse intravascular coagulation, 3; cardiac catheterization, 2; crushed hand, 1; shunt thrombosis, 1; prosthetic heart valve, 1.

We established the following criteria for defining "major" and "minor" complicating events coincident with heparin administration. Major events were defined as death due to hemorrhage, blood transfusion coincident with heparin therapy (excluding transfusions clearly intended for immediate replacement of intraoperative blood loss) and events necessitating premature discontinuation of heparin therapy. All other complications coincident with heparin were classified as minor and included hemoptysis, wound or other hematoma, melena, hematemesis and hematuria. Hematuria was defined as *chronic* if its magnitude before heparin administration was greater than or equal to that during treatment and *acute* if it appeared or increased in magnitude during treatment.

Statistical analyses were done using Student's t tests and chi-squared (x^2) tests with Yates' correction.

Results

Characteristics of the Treated Population

There were 131 patients who met the inclusion criteria; 87 (66 percent) were men. The mean age of the men was 46.4 years (SD equals 16.9) and of the women was 46.7 years (SD equals 16.9).

A total of 81 patients were admitted to medical services and 50 to surgical services. The distribution of patients according to sex and the indications for heparin therapy is given in Table 1. Twenty male patients, 17 below age 35, received

heparin therapy following repair of upper extremity neurovascular lacerations and account for the disproportionate number of men in the arterial surgical procedure group.

All 131 patients received heparin by continuous intravenous infusion via a peristaltic pump device. In 129 of the 131 cases (98.5 percent) an APTT was measured at least once during the course of heparin therapy; in the remaining two, no laboratory monitoring was done.

The mean duration of heparin administration, excluding one patient treated for 73 days, was 8.1 days (SD equals 5.9, range 1 to 31, median 8). In most cases the daily dosage of heparin was altered on one or more occasions in a stipulated attempt to maintain APTT values at between 1½ to 2½ times control values. However, very rarely was the APTT measured more than once a day (in the morning when blood for all ordered tests was drawn). The range between the mean maximum and minimum daily doses was relatively narrow, the mean maximum being 25,600 units (SD equals 5,300, range 12,000 to 43,000, median 24,000); the mean minimum, 19,700 units (SD equals 5,300, range 7,000 to 36,000, median 20,000). On only 20 total patient days was a dosage below 20,000 units per 24 hours used and no patient received this low a dose for more than a day.

Of the 131 patients, 36 percent of the 44 women and 14 percent of the 87 men (P less than 0.01) reported a history of abnormal bleeding (unrelated to heparin therapy) or peptic ulcer disease. Approximately 51 percent of the men and 32 percent of the women had had trauma, an operation or other invasive procedure within ten days before heparin therapy (P greater than 0.05). Twenty-one percent of all patients received one or more intramuscular injections during heparin therapy.

Sixty percent of the patients were given, concurrent with heparin administration, one or more of the following drugs with possible anticoagulant effects: warfarin sodium (49 patients), platelet inhibitory drugs (27), corticosteroids (19) and antineoplastic drugs (5) (37 percent, 21 percent, 15 percent and 4 percent of all patients, respectively).

Of the 131 patients, 70 percent had an APTT measured *before* the start of heparin administration, and 59 percent had a baseline platelet count measured. The mean baseline APTT was 31.3 seconds (SD equals 6.3 seconds, range 17 to 55 seconds and median 31 seconds); the mean baseline platelet count was 234,000 per cu mm (SD equals 91,000, range 18,000 to 424,000 and median 222,000 per cu mm).

BUN and serum creatinine levels were measured before heparin therapy in 85 percent and 83 percent of patients, respectively. The mean BUN level was 19.1 mg per dl (SD equals 15.2 mg per dl); the mean creatinine level, 1.42 mg per dl (SD equals 2.1 mg per dl).

Complicating Events Coincident With Heparin Administration

Major complicating events. Those events classified as major occurred in 13 of the 131 patients (10 percent). The case histories are summarized in Table 2. The specific complications were (two patients had more than one): death in two cases, one definitely due to cerebral hemorrhage and one possibly due to cerebral hemorrhage; events requiring discontinuation of heparin in four cases, and blood transfusion during heparin therapy in nine cases. The mean age of patients having major complicating events was 60.5 years (SD equals 18.8); of patients without such events, 44.9 years (SD equals 18.1), a significant difference (P less than 0.05). Major events coincident with heparin therapy occurred in 22 percent of patients (8/36) 60 years of age or older; in 5 percent of patients (5/95) less than 60 years of age. In all, 6 of 44 women (14 percent) and 7 of 87 men (8 percent) had major complicating events (P greater than 0.05).

Among those with and without major complicating events, statistical analysis disclosed no significant differences in the mean duration of therapy; mean maximum or minimum daily dosage of heparin; trauma, operation or other invasive procedure within ten days, or intramuscular injections or concurrent administration of drugs with possible anticoagulant effect.

Nine patients died. Hemorrhage coincident with heparin administration was the cause of death in one patient and may have been the cause of death in another (cases 1 and 2 in Table 2). In the seven other cases, death was unrelated to hemorrhage (cases 3 through 6, Table 2; cases 14 through 16, Table 3).

Minor complicating events also occurred in 8 of the 13 patients with major events (62 percent). In addition, two patients developed thrombocy-

TABLE 2.—*Summary of All Cases in Which Major Complicating Events Occurred Coincident With Heparin Administration*

Case No.	*Age & Sex*	*Type of Major Complication**	*Indication for Heparin*	*Primary Diagnosis and Intercurrent Disorder(s)*	*Reason for Admission and Clinical Course*	*Concurrent Minor Complications*
1	48 ♂	D,S	PE†	Pituitary adenoma with hypopituitarism; anemia of chronic disease	Resection of pituitary adenoma, complicated by meningitis, hydrocephalus. Four ventriculostomies during heparin therapy for PE; 2 hr after fourth, had seizure activity; CT scan: localized bleeding; heparin discontinued; comatose until death 3 wk later; autopsy denied.	Acute hematuria; fall in hematocrit = 6%
2	73 ♀	D?	Arterial embolization	Acute CVA; atrial fibrillation	Acute embolic CVA. Because of recurrent embolization, heparin initiated despite risk of cerebral hemorrhage; 24 hr later, patient became comatose and remained so until death 2 mo later; CT scans equivocal; autopsy denied.	None
3	70 ♀	S	PE	Acute respiratory failure; severe COPD; CHF with pleural effusion	Respiratory failure. Heparin for suspected PE discontinued due to acute thrombocytopenia. Death from respiratory failure 2 mo later; autopsy: no hemorrhage.	Acute hematuria; fall in hematocrit = 9%
4	88 ♂	S	PE	Metastatic CA of prostate; adenocarcinoma of lung; resected adenocarcinoma of colon; COPD	Urinary retention. Heparin therapy for PE discontinued when patient began having seizures 5 days later; autopsy: intracerebral metastases; no bleeding.	Wound oozing
5	74 ♀	S,T	PE	Severe COPD	Exacerbation of COPD. Heparin for suspected PE discontinued due to acute hematuria and falling hematocrit; transfused with 2 units of packed cells; died from respiratory failure 4 wk later; autopsy: focal hemorrhagic cystitis.	Acute hematuria; fall in hematocrit = 12%
6	78 ♂	T	Prosthetic heart valve	Acute MI with CHF; COPD; anemia of chronic disease	Acute myocardial infarction. Transfused, 2 units of packed cells, to maintain chronically low hematocrit at 30; CHF, dysrhythmias and pneumonia prior to death; autopsy denied.	Chronic hematuria
7	71 ♂	T	DIC	Acute promyelocytic leukemia	Chemotherapy. Evidence of abnormal coagulation prompted treatment with heparin and transfusion with 2 units of blood; discharged in good condition.	Fall in hematocrit = 6%
8	67 ♂	T	PE	Metastatic adenocarcinoma of unknown origin	Ascites. At the completion of heparin therapy, transfused with 2 units of packed cells prior to laparotomy; discharged following chemotherapy.	Fall in hematocrit = 5%
9	64 ♂	T	DVT	Myeloproliferative disease; fever of undetermined origin	Abnormal blood smear. Transfused with 2 units of packed cells after hematocrit value fell to 20%; no obvious source of bleeding; discharged in fair condition.	Acute hematuria; fall in hematocrit = 10%

10	56	♀	T	DVT	Relapsing pancreatitis with common bile duct stricture; scleroderma	Common bile duct stricture. Transfused with 2 units packed cells during heparin therapy for postoperative DVT when hematocrit value fell; discharged in improved condition.	Fall in hematocrit = 5%
11	40	♀	T	DVT	Metastatic ovarian CA	DVT. Transfused with 3 units of packed cells when hematocrit volume fell; discharged in preterminal condition.	Acute hematuria; fall in hematocrit = 5%
12	31	♂	T	DIC	Priapism	Priapism: emergency corpora cavernosa shunt. DIC with purpura fulminans developed postoperatively, treated with heparin and transfused with 3 units of blood; discharged in good condition.	None
13	27	♀	T	DIC	Acute promyelocytic leukemia; Hodgkins' disease	Menorrhagia, seizures and probable DIC. Treatment with heparin, transfusion of 4 units of blood, chemotherapy; gingival bleeding, hematemesis and hematuria; discharged in stable condition.	Acute hematuria; gingival bleeding and hematemesis

*D = death due to hemorrhage, S = heparin administration stopped before anticipated termination, T = transfusion during heparin therapy.
†Other abbreviations: CA = carcinoma; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CT = computerized tomography; CVA = cerebrovascular accident; DIC = diffuse intravascular coagulation; DVT = deep venous thrombosis; MI = myocardial infarction; PE = pulmonary embolism.

topenia and eight had a hematocrit value decline greater than 3 percent.

Minor complicating events. Minor complicating events not associated with major events occurred coincident with heparin administration in 7.6 percent of all cases (10/131) (Table 4). Of these ten patients, three also had a hematocrit value decline greater than 3 percent; ten additional patients not classified as having a minor complication also had declines in hematocrit value of this magnitude. Only one surgical patient had a (small) wound hematoma.

Among those with and without minor complicating events, there were no statistically significant differences in mean age; duration of therapy; maximum or minimum daily dosage of heparin; history of trauma, surgical or other invasive procedure; intramuscular injections, or concurrent administration of drugs.

All complicating events. When patients having either major or minor complicating events coincident with heparin administration were combined, they numbered 23 of the 131 cases (17.5 percent). The mean age of patients having any complicating event was 54.4 years (SD equals 20.0); of patients with none, 44.8 years (SD equals 18.1); this difference is significant (P less than 0.05). Complicating events occurred in 11 of 36 (31 percent) patients above age 60; in 12 of 95 patients (13 percent) under age 60 (P less than 0.05).

There were 13 of the 44 women (30 percent) and 10 of the 87 men (11 percent) who had such events (P less than 0.05). Complicating events occurred in 10 of 28 patients (36 percent) with a history of abnormal bleeding or peptic ulcer disease, versus 13 of 103 patients (13 percent) without such a history (P less than 0.05).

Among those with and without any complicating event, there were no statistically significant differences in the duration or daily dosage of heparin; history of trauma or surgical or other invasive procedure within ten days; intramuscular injection, or concurrent administration of drugs.

Patients With No Intercurrent Disorders

Of the 131 patients, 58 had no acute or chronic diagnosis other than the indication for heparin. No major complicating event occurred among these 58 patients. Two (3.4 percent) experienced minor complicating events: an episode of minor hemoptysis the day after pulmonary embolism (PE) in one; a slightly swollen knee, for which no therapy was required, in the other. In addition,

TABLE 3.—*Summary of Cases in Which Death Following Heparin Administration Was Unassociated With Major Complicating Events*

Case No.	*Age & Sex*	*Indication for Heparin Therapy*	*Primary Diagnosis*	*Reason for Admission and Clinical Course*	*Concurrent Minor Complications*
14	75 ♂	PE	Adenocarcinoma of liver	DVT and PE. Patient ultimately died of acute respiratory failure; autopsy: massive PE with right lung infarction.	None
15	64 ♀	DVT	Metastatic endometrial carcinoma	DVT. Pleural effusions, suspected PE and perforation of the right ventricle during angiography; became comatose 8 days after completion of heparin therapy and died 3 days later; autopsy denied.	Chronic hematuria
16	23 ♂	Arterial thrombectomy	Extensive burns	Burns. Treated with heparin following arterial thrombectomy; sepsis, arterial embolism, pneumonia, ARDS and hypotension before death 6 wk after admission; autopsy denied.	Acute hematuria

PE = pulmonary embolism; DVT = deep venous thrombosis; ARDS = adult respiratory disease syndrome

TABLE 4.—*Distribution of Minor Complicating Events, Acute Thrombocytopenia and Fall in Hematocrit Value, According to Association With Major Complicating Events*

Minor Complicating Events	*Associated With Major Complicating Events* — *No. of Patients*	*Not Associated With Major Complicating Events* — *No. of Patients*
Total patients	8	10
Chronic hematuria	2	4
Acute hematuria	5*	2
Gingival bleeding and hematemesis	1*	..
Wound oozing	1	..
Wound hematoma	..	1
Ecchymoses	..	1
Hemoptysis	..	1
Swollen knee	..	1
Acute thrombocytopenia	2	..
Fall in hematocrit greater than 3%	8	13†

*Patient with gingival bleeding and hematemesis also had acute hematuria.
†Includes ten patients whose hematocrit values fell more than 3 percent associated with neither major nor minor complicating events.

four patients (7 percent) had a fall in hematocrit value greater than 3 percent.

The indications for heparin therapy in this group were: presumed deep venous thrombosis (DVT) (21), presumed PE (13), recent arterial surgical procedure (23) and crushed hand (1).

The patients in this subgroup were younger than the other 73 patients (mean age 39.1 versus 52.4, P less than 0.001); had a lower frequency of a history of abnormal bleeding or peptic ulcer disease (7 percent versus 33 percent, P less than 0.001), but a higher incidence of concomitant use of drugs with anticoagulant effect (29 percent versus 14 percent, P less than 0.05).

Patients Treated for DVT or PE

Of the 87 patients treated for presumed DVT or PE, heparin was discontinued after 24 hours or more in 24 patients when laboratory tests failed to validate the diagnosis. The mean duration of heparin administration among these 24 was 1.8 days (SD equals 0.9). There were no statistically significant differences in mean age, mean maximum or minimum daily dosages of heparin, sex distribution or reported history of abnormal bleeding or peptic ulcer disease between these patients and all other patients in this study. However, they did have significantly lower incidences of trauma, or surgical or other invasive procedures within ten days.

No major complicating events occurred among these 24 patients; a minor complicating event (hematuria) occurred in one.

Among the 63 patients in whom heparin therapy was maintained for DVT or PE, none had a recurrence of venous thromboembolism during hospital stay.

Discussion

This retrospective study gave us an opportunity to assess, in a "nonprotocol" context, two aspects of heparin therapy in a major university hospital: (1) how and for what indications such therapy is applied and how it is monitored (that is, current practices with respect to heparin use) and (2) the type and frequency of complicating events associated with its use.

With respect to current practices in heparin administration, this study was illuminating. For example, it disclosed that in 1979, all physicians involved had adopted continuous and intravenous

administration via a peristaltic pump as their heparin regimen of choice. Neither intermittent intravenous nor subcutaneous methods of administration were used. This finding was unexpected. Indeed, it runs counter to the authors' views, and the published data of others, that intermittent intravenous[15] or subcutaneous[16] administration of heparin are equivalent alternatives. Furthermore, this unanticipated consensus prevented us from achieving one study objective: comparisons of complicating events of different heparin regimens.

Other practice observations also were of interest. Of the multiple tests available for monitoring heparin therapy, only the APTT was used. The way in which it was used was somewhat disquieting in that, in 30 percent of the patients, no APTT measurement was obtained before initiation of heparin. Furthermore, while daily APTT values were obtained in most of the patients during heparin administration, some did not have daily monitoring and two had no APTT test done. Rarely was more than one APTT test done in a 24-hour period. Clearly, then, standard practice at our institution has been to obtain an APTT measurement with the "morning bloods," perhaps adjust the dose when that value returns, and then to make no changes until the next day. In fact, significant changes in dose were relatively uncommon, as reflected by the small differences between the daily minimum and daily maximum of mean heparin dose. The predominant initial order was for 1,000 units per hour (24,000 units a day); adjustments thereafter were quite modest.

It was also clear that the extent of monitoring for complications was variable. For example, it was uncommon for the physician to order daily platelet counts, stool specimen examinations for occult blood or analysis of urine. This may explain, at least in part, the very low incidence of heparin-induced thrombocytopenia. It also influences our rate of minor complications which, therefore, probably represents a *minimum* one.

Equally disquieting to us was the relatively high percentage of patients who received drugs (other than warfarin) with potential anticoagulant effects or who had at least one intramuscular injection during heparin therapy (in both instances, 21 percent).

While such actual clinical data provide useful insights, our report of these practices should not be taken as advocacy. Indeed, we consider omission of an APTT test before and soon after initiation of heparin as a management error, and we cannot condone either the spotty monitoring approach or the concurrent administration of drugs with potential anticoagulant effects. Nevertheless, the data are useful in developing future educative programs. In addition, such data provide the practice context against which the observations regarding complications should be viewed.

Turning next to the major goal of this study—an assessment of the complicating events associated with heparin therapy—our analysis and a review of the literature show that several factors influence the incidence of complications reported and, therefore, the perception of "risk" derived from the data presented. These factors include: the specific method of heparin administration used, the definition of major and minor complicating events and the types of patients treated.

With respect to specific methods of heparin administration, our data can be compared only with those from other series in which continuous intravenous administration of heparin was used.[9-13] These comparative data are given in Table 5. Our 10 percent incidence of major complicating events, 7.6 percent incidence of minor complications without associated major complicating events, with a combined incidence of either major or minor complications of 17.5 percent, all were comparable to previous reports.[9-13]

While such comparisons are useful, it should be noted that the definitions of major and minor complications are not uniform among the series (Table 5). For example, the highest incidence of major bleeding was reported by Mant and coworkers[12] who included a fall in hemoglobin value of greater than 2 grams per dl as a major complication. Thus, variations in definition can heavily influence the reported major and minor percentages, and it behooves physicians to examine these definitions with care.

Our own definition of major consequences was as rational and as arbitrary as the rest: death due or possibly due to hemorrhage, transfusion and premature interruption of therapy. Yet neither our "major complicating events" nor those reported in other series necessarily imply that heparin was responsible. For example, we found it impossible to determine whether a transfusion would have been required in a given patient had heparin not been administered, because most had concomitant problems that may have led to the need for transfusion. The same is true for those patients in whom a decision to interrupt heparin therapy is considered a major complicating event. There-

fore, all such patients were included with those having had a major complicating event. Similar considerations apply to the minor complicating events reported by ourselves and others. For example, we excluded hematocrit declines in value of more than 3 percent as *minor complications* because their relationship to heparin versus other concurrent events (including blood loss for laboratory tests) was obscure and because a review of 100 consecutive medical patients not receiving heparin disclosed that variations of this magnitude occurred in more than 30 percent.

Despite these problems, several things regarding complicating events during heparin therapy seem clear. First, deaths due to hemorrhage are rare. Of the 534 patients in Table 5, three deaths attributable to heparin are reported (0.56 percent); all three were secondary to intracerebral bleeding. In our series, the one definite heparin-related death occurred when a ventriculostomy was done in a patient receiving heparin; the other possibly heparin-related death occurred when, despite known risk, a patient with presumed cerebral thrombosis was given the drug. Such judgment hazards do not reflect on the inherent risk of the agent per se in otherwise normal persons.

Our analysis also has provided new data regarding an often-neglected factor that clearly influences the incidence of complications; namely, that many patients to whom heparin is given have serious concomitant disorders. Every major complicating event in our series occurred in a patient with severe intercurrent disease: three with leukemia or myeloproliferative disease, three with metastatic carcinoma, three with severe chronic cardiac or pulmonary decompensation, three with diffuse intravascular coagulation, one with an acute cerebrovascular accident (CVA) and one with meningitis in whom multiple ventriculostomies were done.

In contrast was our experience in the 58 patients who had no acute or chronic illness other than that which led to heparin therapy. Among this subgroup, no major and two minor compli-

TABLE 5.—*Results of Six Series in Which Continuous Intravenous Administration of Heparin Via Infusion Pump Was Used*

Series	No. of Patients	Major Complications		Minor Complications		Total Complications	Death Due to Hemorrhage
		Definition	No. (Percent)	Definition	No.* (Percent)	No. (Percent)	No. (Percent)
Basu et al[9]	234	Transfusion required; heparin discontinued because of bleeding.	8(4.0)	No treatment needed.	11(5.0)	19(8.0)	0
Salzman et al[10]	69	Transfusion required; heparin discontinued because of bleeding; hospital stay prolonged because of bleeding.	1(1.0)	All other bleeding.	18(26.0)	19(27.0)	1(1.0)
Glazier and Crowell[11]	20	Death; transfusion required; heparin discontinued because of bleeding.	0	Fall in hematocrit less than 4 ml/100 ml; no transfusion or cessation of therapy required.	6(30.0)	6(30.0)	0
Mant et al[12]	40	Transfusion required; heparin discontinued because of bleeding; fall in hemoglobin greater than 2 gm/dl.	6(15.0)	All other bleeding.	6(15.0)	12(30.0)	0
Wilson and Lampman[13]	40	Transfusion required; heparin discontinued because of bleeding; hospital stay prolonged because of bleeding.	2(5.0)	All other bleeding.	3(8.0)	5(13.0)	0
This study	131	Death due to hemorrhage; transfusion required; heparin discontinued.	13(10.0)	All other bleeding.	10(8.0)	23(18.0)	2(2.0)
TOTALS	534		30(5.6)		54(10.1)	84(15.7)	3(0.6)

*Includes only minor complications without concurrent major complications.

cating events occurred. Thus, in patients without intercurrent disease, we found the risks associated with heparin therapy were quite low.

This same situation was evident in another important subgroup—the 24 patients in whom heparin was started because a diagnosis of DVT or PE was entertained but subsequently not confirmed. This is a relatively common practical strategy. Among these 24 patients, no major complications and one minor complication occurred.

Our data do support the previously reported associations of major complicating events with increased age, particularly age greater than 60 years,[17-19] and in women. However, it is difficult to dissociate age from the impact of intercurrent disease, which is also more frequent in the over-60 age group. Another important observation is that we (like others) found no relationship between complications and heparin dose,[9-17] although our dose range was at the lower end of those used in other studies. Our study did not deal with the equally complex question of the most efficacious regimen, although clinical thromboembolic recurrence did not occur in any patient treated.

Conclusions

These data lead us to several conclusions. Without advocacy by the authors or their colleagues, continuous intravenous infusion by peristaltic pump, monitored by daily APTT determinations, has become the almost exclusive mode of heparin therapy at our hospital. Major and minor complicating events associated with this regimen are concentrated in patients who have significant intercurrent disease and are older than 60. However, among patients without intercurrent disease, major complications did not occur and minor complications were rare. Our data do not support contentions that heparin is the "leading cause of adverse drug reactions in hospital patients"[20] and is "the drug responsible for a majority of drug deaths in patients who are *reasonably healthy*."[6] Indeed, our data indicate that continuous intravenous administration of heparin poses extremely limited risk in patients free of disease other than the one being treated with heparin. Because decisions regarding the most appropriate diagnosis-treatment sequence in patients with thromboembolism are conditioned by perception of the risks posed by heparin therapy, additional data dealing with this question are needed.

REFERENCES

1. Thomas DD: Heparin in the prophylaxis and treatment of venous thromboembolism. Semin Hematol 1978; 15:1-17

2. The urokinase pulmonary embolism trial—A national cooperative study. Circulation 1973; 47 and 48(Suppl 2):1-108

3. Sharma GVRK, Burleson VA, Sasahara AA: Effect of thromboembolytic therapy on pulmonary-capillary blood volume in patients with pulmonary embolism. N Engl J Med 1980; 303: 842-845

4. Hirsh J, Hull R: Comparative value of tests for the diagnosis of venous thrombosis. World J Surg 1978; 2:27-38

5. McNeil BJ: Ventilation-perfusion studies and the diagnosis of pulmonary embolism: Concise communication. J Nucl Med 1980; 21:319-323

6. Robin ED: Overdiagnosis and overtreatment of pulmonary embolism: The emperor may have no clothes. Ann Intern Med 1977; 87:775-781

7. Moser KM: Pulmonary embolism: State of the art. Am Rev Resp Dis 1977; 115:829-852

8. Chin HM, Hirsh J, Yung WL, et al: Relationship between the anticoagulant and antithrombotic effects of heparin in experimental venous thrombosis. Blood 1977; 49:171-184

9. Basu D, Gallus A, Hirsh J, et al: A prospective study of the activated partial thromboplastin time. N Engl J Med 1972; 287: 324-327

10. Salzman EW, Deykin D, Shapiro RM, et al: Management of heparin therapy. N Engl J Med 1975; 292:1046-1050

11. Glazier RL, Crowell EB: Randomized prospective trial of continuous versus intermittent heparin therapy. JAMA 1976; 236: 1365-1367

12. Mant MJ, O'Brien BD, Hong KL, et al: Hemorrhagic complications of heparin therapy. Lancet 1977; 1:1133-1135

13. Wilson JR, Lampman J: Heparin therapy: A randomized prospective study. Am Heart J 1979; 97:155-158

14. Pitney WR, Pettit JE, Armstrong L: Control of heparin therapy. Br Med J 1970; 4:139-141

15. Wilson JE, Bynum LJ, Parkey RW: Heparin therapy in venous thromboembolism. Am J Med 1981; 70:808-816

16. Bentley PG, Kakkar VV, Scully MF, et al: An objective study of alternative methods of heparin administration. Thromb Res 1980; 18:177-184

17. Jick H, Slone D, Borda IT, et al: Efficacy and toxicity of heparin in relation to age and sex. N Engl J Med 1968 Aug 8; 279:284-286

18. Vieweg WVR, Piscatelli RL, Houser JJ, et al: Complications of intravenous administration of heparin in elderly women. JAMA 1970 Aug 24; 213:1303-1306

19. Kernohan RJ, Todd C: Heparin therapy in thromboembolic disease. Lancet 1966; 1:621-623

20. Porter J, Jick H: Drug-related deaths among medical inpatients. JAMA 1977; 237:879-881

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Cerebellar Hemorrhage as Evaluated by Computerized Tomography

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Nine patients with cerebellar hemorrhage were examined initially with computerized tomographic (CT) scanning. CT appearance in combination with clinical state determined therapy. The most common presenting symptoms were headache, ataxia and vomiting, usually with alterations in the level of consciousness. Three patients were comatose. In five patients surgical evacuation of the hematoma was done and one of these died. Two who were moribund at presentation were not operated on and succumbed. The remaining two did not require operation and recovered. Early investigation with CT scanning considerably aided decisions as to the approprate method of treatment.

BEFORE 1960 cerebellar hemorrhage was rarely diagnosed ante mortem and, when diagnosed, the results of surgical procedures were discouraging.[1-3] With delineation of the characteristic clinical picture, considerable improvement in diagnosis and treatment resulted.[4,5] Cerebellar hemorrhage was almost always fatal without prompt surgical intervention.[2,5,6] The standard recommendation was that the diagnosis be made on the basis of history, neurologic examination findings and the presence of blood in the spinal fluid on lumbar puncture, with specific recommendation against delaying surgical decompression to perform neuroradiologic procedures.[1,5,6] In this paper we report that the advent of computerized tomographic (CT) scanning has changed these recommendations. A population of patients with cerebellar hemorrhage not requiring surgical decompression can be identified; the delay engendered to obtain a CT scan when immediately available does not compromise the results of subsequent treatment. In addition, a CT scan can identify cerebellar hemorrhage in patients with atypical or nonlocalizing presentation, increasing diagnostic accuracy.

Description of Cases

Nine adult patients with CT-documented cerebellar hemorrhages measuring 3.0 sq cm or more in largest cross-sectional area were included in this series. These patients were seen during an 18-month period at the University of Washington Hospitals, and ranged in age from 45 to 81 years at the time of presentation. There were five men and four women. The most common presumed cause of cerebellar hemorrhage was hypertension. Systolic blood pressure was elevated at some point

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TABLE 1.—*Eventual Outcome Correlated With Clinical Presentation and Hematoma Size in Nine Cases of Cerebellar Hemorrhage*

*Case No.**	*Age*	*Level of Consciousness†*	*CT Clot Size (sqcm)*	*Hydrocephalus*	*Operation*	*Outcome§*	*Presumed Cause of Clot*
1	57	Comatose	12.1	Pronounced‡	No	Patient died	Unknown
2	67	Alert	8.4	Mild	Yes	Excellent	Hypertension, anticoagulation
3	63	Obtunded	8.0	Mild	Yes	Patient died (rebleed)	Hypertension
4	65	Alert	7.5	None	Yes	Excellent	Hypertension
5	77	Comatose	4.9	Pronounced‡	No	Patient died	Hypertension
6	81	Alert	4.3	Moderate	Yes	Good	Hypertension
7	45	Comatose	4.3	Mild	Yes	Excellent	Traumatic‖
8	53	Alert	3.3	None	No	Good	Hypertension, ? traumatic
9	72	Alert	3.0	Mild	No	Good	Hypertension

*The cases are ranked according to size of cross-sectional area of clot as measured on CT scan.

†The level of consciousness is defined as the response to voice commands. The patients presenting in coma were not responsive to deep pain.

‡Hydrocephalus was measured from the size of the lateral ventricles. Both cases with pronounced hydrocephalus had intraventricular hemorrhage.

§The outcome is defined in terms of immediate survival and long-term residual neurologic deficit.

‖The intraparenchymal cerebellar clot in this case clearly predated the trauma responsible for the subdural and epidural hematoma encountered at the time of surgical decompression, and was isodense on the initial CT scan. The clot was liquid at operation and appeared most likely spontaneous in origin.

in the course of seven patients. Trauma was a probable cause of hemorrhage in one patient and another had no known reason for hemorrhage. The presenting symptoms consisted of coma of unknown origin in three cases, headaches and vomiting in five, appendicular or gait ataxia in three and vertigo in one. Five patients were alert when first examined, one was obtunded and three were comatose (no response to voice commands). As defined in Table 1, the level of consciousness appeared to be one of the better indicators of outcome; three out of four with an altered level died.

The patients who were alert enough to speak indicated a sudden onset of symptoms in all cases. On examination, this group of patients (six of nine) showed appendicular or gait ataxia (four of six), lateral conjugate gaze palsy (two of six), hemiparesis (two of six) and dysarthria (two of six). All had reactive pupils. Two of the three comatose patients were unresponsive to pain and one showed decerebration and unreactive pupils. Thus, the typical symptomatology for the alert patients consisted of headache, vomiting and dizziness, with neurologic findings of unilateral or truncal ataxia. The comatose patients showed only diffuse and nonspecific findings.

CT scans were performed on a GE 8800 scanner, except for one scan from an EMI machine. On transverse cuts through the posterior fossa, the section with the largest cross-sectional area of hemorrhage was chosen for measurement. It was measured either by the scanner or by approximating the lesion as an ellipse. These measurements were then referred back to the original head size and expressed in square centimeters. The volume of the hemorrhage could not be estimated as reliably because of partial-volume effects, so this value was not included. Table 1 correlates the

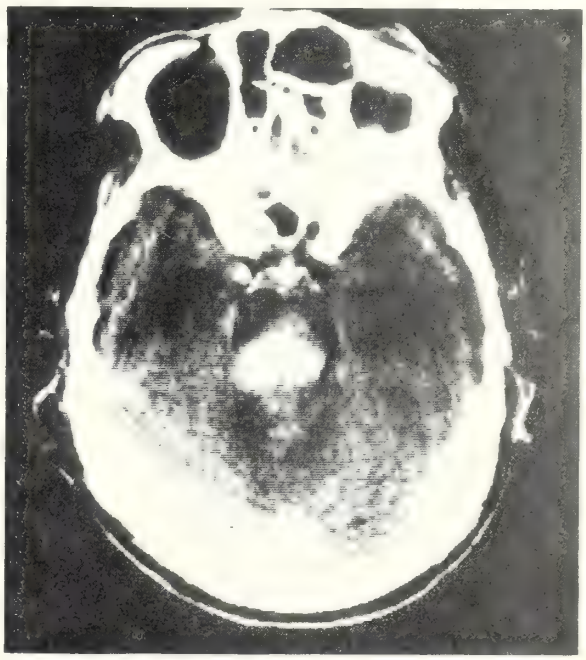

Figure 1.—Posterior fossa CT scan of case 5 in Table 1. The essentially midline hematoma extends superiorly to the tentorial hiatus and inferiorly to the foramen magnum. The clot on this cut is restricted to the midline cerebellum and ventricular system.

eventual outcome with clinical presentation and total area of clot.

A patient's symptoms and the findings on CT scan were all taken into account in determining further therapy. For two of the comatose patients (cases 1 and 5 in Table 1) the CT scan showed midline hemorrhage and rupture of the hemorrhage into the ventricular system (Figure 1). Both of these patients also had pronounced hydrocephalus. These CT findings correlated with the premorbid clinical condition, and neither patient underwent surgical decompression; both patients soon died. CT scans in all of the other patients showed laterally located hematomas, often extending far out into the cerebellar hemisphere, but with no ventricular rupture and only minimal hydrocephalus (Figure 2). The two patients with the smallest clots (cases 8 and 9 in Table 1; Figure 3) received only medical therapy; both eventually recovered satisfactorily with only minimal residual ataxia.

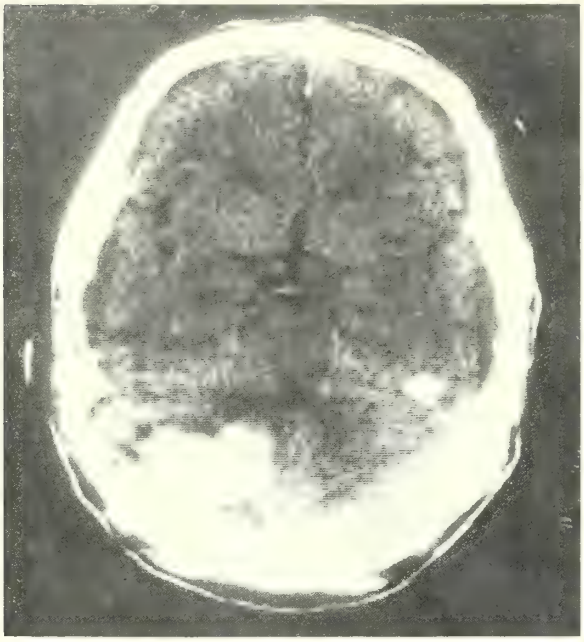

Figure 2.—Posterior fossa CT cut from case 4. The scan shows a relatively large but restricted hematoma in the right lateral cerebellar hemisphere. The more midline aspect extends approximately to the dentate nucleus on the right side.

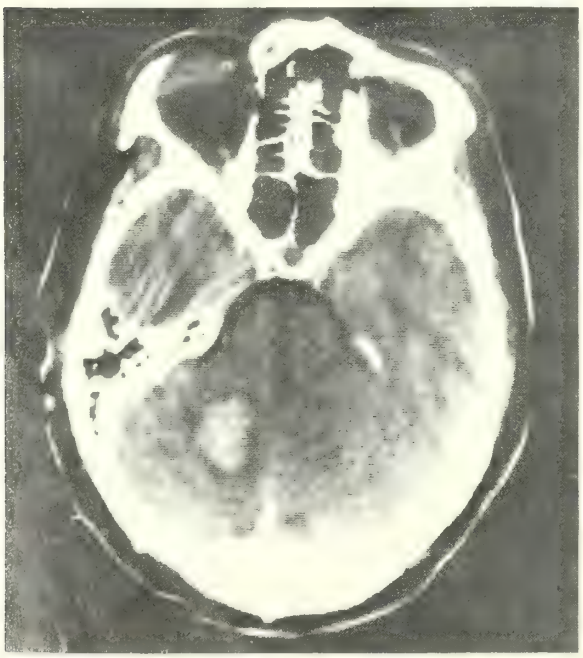

Figure 3.—CT scan from case 9, Table 1. The clot on this posterior fossa section is located within the hemisphere and is relatively small, compared with Figure 2. This patient did not require surgical decompression.

On the basis of symptoms and neurologic examination, the other five patients (cases 2, 3, 4, 6 and 7 in Table 1) were considered candidates for a surgical procedure. Thus, a unilateral posterior fossa craniectomy, with complete suction evacuation of the hematoma, was done on all five patients. Four had freshly clotted blood in the hematoma cavity, while one patient had a partially liquefied clot of indeterminate age and a fresh clot in the subdura of the posterior fossa (case 7 in Table 1). Though the patients were referred as soon as possible after initial evaluation, the time lapse from onset of symptoms to operation was variable, from 6 to 72 hours. On examination no patient was found to worsen during this preoperative period, partly due to treatment with mannitol (1 gram per kg given intravenously) and steroids (dexamethasone sodium phosphate, 24 mg per day). Four of these five patients recovered, with only minimal residual ataxia after three months. One patient suffered a hypertensive crisis immediately after operation and subsequently a subarachnoid hemorrhage developed. This patient died seven days postoperatively.

Analysis

Three groups of patients are defined by this study, similar to groups outlined by previous authors.[1,5,7] The first group consists of immediately devastated patients with larger, more midline clots on the CT scan (Figure 1). Because of poor neurologic function, these patients did not have a surgical procedure. The second group had medium-sized hematomas and were quite sympto-

matic though generally they retained consciousness. These patients probably required the surgical decompression of the clot to avert significant brain-stem compression (Figure 2). The third group consists of those patients with milder symptoms, longer times to presentation and small clots (less than 4 sq cm) seen on CT scan (Figure 3). In these patients the clot appears to resolve without surgical intervention and, most important, critical brain-stem compression does not develop. As illustrated by case 7 (Table 1) some patients do fall outside of these boundaries. This patient had coma, skew deviation of the eyes and decerebration, yet results were complicated on a CT scan and there was a significant ethanol level (550 percent). The CT scan in this case showed almost isodense intraparenchymal hematoma in the cerebellar hemisphere, loss of the fourth ventricular outline, subdural hematoma over the superior aspect of the cerebellum and epidural hematoma laterally in the posterior fossa. All three varieties of hematoma were confirmed and removed at operation, but the origin of the older intraparenchymal hematoma was not clear. However, the patient quickly recovered consciousness and excellent neurologic function. This represents an isolated case of good neurologic recovery following a densely comatose state.[8,9]

Discussion

Early diagnosis and proper treatment of cerebellar hemorrhage may lead to improved outcome.[1,4,6,7,10,11] Before the common use of the CT scan, most authors felt cerebellar hemorrhage was uniformly fatal if not immediately decompressed surgically. The delay engendered in doing angiography, ventriculography or pneumoencephalography not only was unacceptable, but the procedures themselves could be extremely risky and at times nondiagnostic.[1,2,4,6] CT scanning, however, appears reliable and expeditious in achieving the radiological diagnosis of posterior fossa hematoma.[7,11,12] In the present study, no patient deteriorated during the time required for radiological confirmation of the clinical diagnosis. Two patients with cerebellar hemorrhage did not require surgical procedures, showing that there is a population of patients with cerebellar hemorrhage in which it is not fatal.[7] The comatose patients with nonlocalizing histories and neurologic examinations were accurately diagnosed, one of whom benefited from surgical decompression. Consequently, the information obtained from the CT scan proved quite helpful in integrating clot size and extent of spread with either surgical or medical management. The value of the information far outweighed the potential hazards of delaying surgical therapy.

In contrast to pathological studies,[2,10] few cases of overt cerebellar infarction were found during this 18-month period of evaluation. Many patients suspected of having brain-stem or cerebellar infarction underwent CT scanning, but no case of mass effect without hematoma in the cerebellum was found. Because the incidence of pathological cerebellar infarction with mass effect may be as high as hemorrhage in the same location,[13] this bias may be partially attributable to the limitations of CT scanning in detecting relatively small changes in tissue density.

The three groups of patients outlined here are similar to those previously defined by McKissock and co-workers.[1] However, in the previous study, the much longer time to presentation may have been responsible for the more frequent progression to loss of consciousness. In a recent study by Little and colleagues,[7] approximately the same groups of patients were examined. The overall mortality in that study was 20 percent, somewhat lower than the 33 percent found in the present one. This difference may be due to their larger number of patients harboring smaller hematomas, though it is difficult to compare their diameter measurement[7] with the cross-sectional area presented here. But, in both the study by Little and associates[7] and the present experience, hematoma size as measured from the CT scan has proved important in planning further therapy. Thus, the size of the hematoma, potential mass effect, rupture into the ventricular system and hydrocephalus may be correlated closely with the clinical presentation.

It is difficult to decide whether the more rapid time to presentation or the increased diagnostic accuracy with CT scanning may account for the overall improvement in outcome, as compared with earlier studies.[1-6] The patients with immediate and devastating neurologic damage who are not surgical candidates, and those patients with smaller hematomas not requiring operative decompression, are certainly more easily assigned therapy following a CT scan. But outcome in these two groups of patients is relatively unaffected by this initial screening. It remains important to identify early, before a change in the

level of consciousness, those patients who would benefit from craniotomy and hematoma evacuation. Quantitative estimation of clot size, mass effect and ventricular enlargement by CT scanning may contribute positively to the outcome of this group of patients.

REFERENCES

1. McKissock W, Richardson A, Walsh L: Spontaneous cerebellar hemorrhage—A study of 34 consecutive cases treated surgically. Brain 1960 Mar; 83:1-9

2. Dinsdale HB: Spontaneous hemorrhage in the posterior fossa. Arch Neurol 1964 Feb; 10:200-217

3. Norris JW, Eisen AA, Branch CL: Problems in cerebellar hemorrhage and infarction. Neurology 1969 Nov; 19:1043-1050

4. Fisher CM, Picard EH, Polak A, et al: Acute hypertensive cerebellar hemorrhage: Diagnosis and surgical management. J Nerv Ment Dis 1965 Jan; 140:38-57

5. Ott KH, Kase CS, Ojemann RG, et al: Cerebellar hemorrhage: Diagnosis and treatment. Arch Neurol 1974 Sep; 31:160-167

6. Brennan RW, Bergland RM: Acute cerebellar hemorrhage—Analysis of clinical findings and outcome in 12 cases. Neurology 1977; 27:527-532

7. Little JR, Tubman DE, Ethier R: Cerebellar hemorrhage in adults—Diagnosis by computerized tomography. J Neurosurg 1978 Apr; 48:575-579

8. Yoshida S, Sasaki M, Oka H, et al: Acute hypertensive cerebellar hemorrhage with signs of lower brainstem compression. Surg Neurol 1978 Aug; 10:79-83

9. Sokol JH, Rowed DW: Traumatic intracerebellar hematoma. Surg Neurol 1978 Nov; 10:340-341

10. Sypert GW, Alvord EC: Cerebellar infarction—A clinicopathological study. Arch Neurol 1975 Jun; 32:357-363

11. Mauersberger W, Fuchs EC: The value of computerized axial tomography (CAT) in early diagnosis of intracerebellar hemorrhage in children. Mod Probl Pediatr 1977; 18:97-100

12. Müller HR, Wüthrich R, Wiggli U, et al: The contribution of computerized axial tomography to the diagnosis of cerebellar and pontine hematomas. Stroke 1975 Sep—Oct; 6:467-475

13. Woodhurst WB: Cerebellar infarction—Review of recent experiences. Can J Neurol Sci 1980 May; 7:97-99

Educational Material on Large Bowel Cancer

THE EXHIBIT and brochure *Large Bowel Cancer: Biology and Control* are still available for distribution. A joint undertaking of the National Large Bowel Cancer Project and the American College of Surgeons, they are divided into three topics, "Finding the Cause," "Current Management" and "Toward a Solution." The three-panel exhibit and the 36-page brochure are particularly suited for teaching seminars, national meetings and workshops on cancer of the large bowel.

The exhibit and copies of the brochure can be obtained separately or together, free except for shipping charges. For a description and further information contact Mrs. Irene J. Diament, Administrative Assistant, Cancer Department, American College of Surgeons, 55 East Erie Street, Chicago, IL 60611 (312) 664-4050.

Refer to: Owsley JQ Jr: Cosmetic surgical procedures for the aging face. West J Med 136:203-210, Mar 1982

Cosmetic Surgical Procedures for the Aging Face

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In the past decade there has been a remarkable increase in the number of patients having cosmetic operations to achieve a more youthful appearance. Demographic, social and economic factors in our society have contributed to this phenomenon, along with an increase in the number of trained plastic surgeons. Moreover, there recently have been major technical advances in aesthetic surgical procedures, including innovations in anesthetic techniques. The newer procedures for forehead-plasty, blepharoplasty and face lift are based on improved understanding of the facial anatomy. The operations are more complex and extensive, but experience has shown that they can be done safely. Correction of the changes of facial aging has been enhanced and the duration of the result has been prolonged.

DURING THE PAST TEN YEARS, plastic surgeons have noted a remarkable increase in requests for operations to correct facial changes associated with aging. Among plastic surgeons, the 1970's have come to be referred to as the decade of the face lift. This paper reviews several factors, including technical advances, that have contributed to the increase in cosmetic facial operations.

Demographic Considerations

A "youth-oriented" culture began developing in the 1960's, perhaps starting with the election of John F. Kennedy. At his inauguration as President, Kennedy declared that a new generation of Americans, aware of its youth and vitality, had emerged at the forefront with him, prepared to manage the affairs of the country. His seductive appeal had a far-reaching impact.

The Kennedy years were followed in the late 1960's by a substantial demographic change in the United States, occurring as the post-World War II baby boom introduced a vast group of young Americans into the social, political and business life of the country. Since that time, the communications media have steadily conveyed the message that to be young and healthy is to be able to compete and succeed.

Getting into and staying in shape, or at least having that appearance, has become a major obsession in our society. The resultant peer pressure has been felt by Americans of all ages. Concomitantly, advances in general health-care delivery and greater attention to improved nutrition and dietary habits, along with emphasis on exercise, have resulted in a general population that is stronger and feels younger. However, not all of us were young in the 1960's and 1970's, and the signs of facial aging that betray the passage of youth cannot be staved off by improved health care or exercise. For many people this aging appearance signals a loss of self-confidence and decreased ability to compete.

Before the 1970's, plastic surgical procedures to correct facial aging existed in a very narrow world. Face-lift and eyelid operations were mainly done on members of the highest echelons of society or of the theatrical profession, for whom it was considered appropriate for career purposes.

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ABBREVIATION USED IN TEXT

SMAS = superficial musculoaponeurotic system

There were comparatively few plastic surgeons and those surgeons who did a lot of aesthetic facial operations practiced mostly in the capitals of society and of the performing arts, specifically in New York City and Los Angeles. Most commonly, a rich person from an outlying area traveled to the plastic surgeons in New York or Los Angeles for facial cosmetic operations.

In the years after World War II, plastic surgery as a subspecialty came of age with rapidly increasing participation of plastic surgeons in medical school and postgraduate medical education. As plastic surgeons moved into the mainstream of academic surgery, a greater number of medical students interested in the surgical field were exposed to the multifaceted specialty of reconstructive and aesthetic surgery. The demand for training in plastic surgery brought about the development of residency training programs in nearly every major university medical school in the country and a number of private hospitals with academic orientation.

Approximately 100 new surgeons trained in plastic and reconstructive surgery become eligible for specialty certification in the United States each year. There are now about 2,500 plastic surgeons, either certified or eligible for certification by the American Board of Plastic Surgery, which represents nearly a fivefold increase since 1960. Most still practice in major metropolitan areas, but there are many well-trained, well-qualified plastic surgeons who are doing aesthetic surgical procedures in the smaller communities throughout the United States. This is particularly true in the state of California where there are more than 400 practicing plastic surgeons.

Another important factor contributing to the increase in aesthetic operations relates to the increasing affluence of our society. The past 20 years have seen the wealth of our nation provide discretionary income to a wide spectrum of the population that can now afford second automobiles, vacation homes, travel abroad and, with increasing frequency, aesthetic surgery. To the rich, socially prominent and show business patient groups, we have added middle-class housewives, professional women and, increasingly, business and professional men. The common factor that links all of these groups of patients is that they wish to maintain a personal appearance that is consistent with the youthful and even athletic image that has become a basic social and professional factor in American life.

Advances in Anesthesia

Yet another consideration to be discussed are the technical advances that have occurred in the field of aesthetic surgery. These include important innovations in anesthesia techniques. It is of historical interest to observe certain traditional differences in the choice of anesthesia for facial aesthetic operations as practiced on the East and West Coasts. In New York City, the early center for aesthetic surgery, health insurance plans have included coverage for hospital care and anesthesia administration for cosmetic operations. Consequently, most New York patients and surgeons choose general anesthesia for aesthetic facial surgical procedures and patients customarily convalesce for several days in the hospital after the operation. In the West, health insurance policies have always excluded any benefits for cosmetic surgery and, furthermore, until recently hospital beds were in relatively short supply in the metropolitan areas of the West Coast. Face lifts and eyelid procedures were typically done on an outpatient or short-stay basis in a hospital or a private clinic. Of necessity, they were done under local anesthesia.

Before the 1970's local anesthesia for cosmetic operations of two to four hours' duration was often an uncomfortable experience. Preoperative sedation was administered with caution for fear of overdepressing the patient and was usually limited to medication given orally or by intramuscular injections. Narcotics such as morphine sulfate and meperidine hydrochloride (Demerol) often produce the uncomfortable and complicating side effects of nausea, with intraoperative or postoperative vomiting.

The introduction of diazepam (Valium) in the early 1970's revolutionized local anesthetic techniques for plastic surgery. Diazepam, administered in small doses intravenously in conjunction with incremental doses of narcotics such as meperidine or fentanyl citrate, produces a rapid sedation characterized by euphoria and drowsiness, often leading to a sleeping state from which a patient can be easily aroused by voice command. During this period of sedation, local anesthetic infiltration or nerve block can be done without disturbing the

patient. An additional benefit of diazepam is that of amnesia for the episode of surgery.

Respiratory depression is much less frequent with diazepam than with barbiturates. The combined administration intravenously of diazepam with small doses of narcotic allows a patient to have an operation with local anesthesia of three to four hours' duration with complete relaxation and comfort and then to recover with little or no memory of the event. Patients contemplating a cosmetic surgical procedure with local anesthesia can be reassured that "they will be asleep" when, in fact, they will not be deeply anesthetized.

Certain tranquilizers such as prochlorperazine (Compazine) or droperidol (Inapsine) can be used to suppress narcotic-induced nausea and vomiting. For that matter, the newer synthetic narcotics such as fentanyl rarely cause patients to become nauseated. Compazine or, in selected cases, chlorpromazine hydrochloride (Thorazine),[1] may be used intraoperatively to control transient labile hypertension, which is a problem in patients undergoing a facial surgical procedure. Controlling hypertension and vomiting greatly diminishes intraoperative bleeding and the possibility of postoperative hematoma or prolonged ecchymosis.

Facial Aesthetic Surgical Procedures

At the annual meeting of the American Society of Plastic and Reconstructive Surgeons in 1976, it was stated that facial aesthetic surgical techniques had been almost completely revolutionized in the preceding ten years.[2] Plastic surgeons throughout the country are using procedures that were developed in the 1970's. These operations for the most part result from detailed analysis and understanding of eyelid and facial anatomy and the changes that occur with aging. The newer procedures are more extensive and sophisticated but experience has proved that they can be done with a high degree of safety and will provide improved and longer lasting results.

Forehead-plasty

Until recently, forehead *lifts* were not favorably regarded by plastic surgeons in the United States and were seldom done. Direct brow lift by local forehead skin excision has been commonly done when warranted but has the disadvantage of leaving visible scars in the brow and temple.[3] Disinterest in the forehead-lift operation was probably related to misconceptions regarding the functional anatomy of the forehead brow region and inadequate surgical approaches to the problems of this area.

Along with the face and neck, the forehead tissues lose elasticity, elongate and sag with advancing age. In the forehead this drooping is most noticeable in the brow and glabellar regions, where drooping eyebrows impinge on the orbit and reduce the dimension of the orbital-eyelid space. In an attempt to lift the drooping brows and upper eyelid, a contracture of the frontalis muscle in the forehead often develops that results in transverse wrinkling of the forehead, eventually leaving deep lines. Glabellar frown lines are etched by the chronic squinting process associated with reading at work or as a reaction to bright sunlight when out of doors.

In the past, a forehead-lift operation was done primarily to eradicate the transverse forehead lines. The technique was directed to increasing vertical skin tension with frontal scalp excisions, which often produced excessive elevation of the anterior hairline, wide scars, occasional hair loss and frequently excessive elevation of the eyebrows, creating a surprised expression.[4] Early recurrence of the transverse lines was common and thus the forehead-plasty fell into disrepute.

American plastic surgeons are indebted to Kaye[5] for clarifying the anatomic problems of the forehead and describing a more appropriate operation for correction of forehead relaxation. The present-day forehead-lift procedure is specifically directed to elevating drooping eyebrows. To accomplish this, it is now recognized that the most important factor in the operation is to completely free dense fascial attachments between the skin of the brow region and the superior orbital rim and frontonasal area so that the brows can be elevated without skin tension. Glabellar frown lines are diminished by appropriate resection of the corrugator muscles and occasionally by incising the subcutaneous tissue adjacent to the frown lines from the deep aspect of the forehead flap, which smooths the glabellar skin by appropriate lateral tension on the elevated forehead flap. An additional important part of the operation is the segmental resection of a portion of the frontalis muscle, which reduces tension in the flap, allowing the brow to be raised with less skin resection required so that the frontal hairline is not elevated excessively. Dividing the frontalis muscle and correcting the brow and upper lid overhang minimizes the tendency for recurrence of the deep transverse wrinkles.

In the past four years I have included a forehead-plasty in almost a third of the operations done for correction of changes due to facial aging. Using this approach for forehead lift has resulted in a high degree of satisfaction to patients, who have expressed pleasure regarding the results in this area particularly. The maintenance of this correction is comparable with that of the face and the neck.

Blepharoplasty

Cosmetic blepharoplasty is the most popular and frequently done procedure for improvement of facial aging problems. It is the cosmetic operation most commonly done in men though face lifts in men are being done with increasing frequency. Complementary blepharoplasty is done in approximately 70 percent of the patients who have a face lift.

Blepharoplasties were originally done by ophthalmologists primarily to eliminate grossly excessive upper eyelid skin that produced obstruction to vision by lateral hooding over the lid margins. Aesthetic correction of additional deformities underlying the skin, including redundancy of muscle and fat, was suggested by plastic surgeons who recognized the contribution of these tissues to the aging appearance of the eyelids. Bames[6] of Los Angeles called attention to the protrusion of orbital fat into the eyelids which produces the baggy-eyelid appearance. His colleague and associate, Castanares,[7] published a detailed anatomical study of the orbital fat pads and their contribution to eyelid deformities. After many contributions to the technique of cosmetic blepharoplasty, Dr. Castanares has come to be regarded as the originator of modern cosmetic eyelid operations.

More recently, the importance of selective resection of redundant portions of the orbicularis muscle has been emphasized.[8,9] Owsley first reported in 1980 that the presence of a submuscular fat pad in the upper eyelid overlying the lateral orbital rim contributes to the bulky lateral hooding appearance.[10] Resection of this fat pad, along with an overlying strip of orbicularis muscle, has enhanced the correction of such deformities.

In certain patients, predominantly Orientals, there is a minimal attachment of the pretarsal skin of the upper lid to the underlying orbicularis muscle and tarsus, which leaves the skin loose and without a well-defined palpebral crease.[11] To create a well-defined crease and fold (that is, a westernized eyelid), suture fixation between the skin and the supratarsal orbital septum has proved effective. Various technical variations of the procedure have been described.[12-15] Modern cosmetic blepharoplasty has become complex and time-consuming. Such operations require detailed knowledge of anatomy and painstaking attention to technique. The advantage of these procedures is the improved and longer lasting correction of the aging appearance of the eyelids.

Face Lift

The face-lift operation has undergone perhaps the greatest transformation of any of the facial cosmetic procedures. The so-called classical face-lift operation that originated in Europe in the early part of the century involves the separation of the skin of the face and neck from the superficial subcutaneous tissues with incisions that begin in the temporal scalp, encircle the ear and extend into the cervical and occipital hair-bearing regions. Variations in location of incision, extent of skin undermining and pattern of resection of the superiorly advanced skin redundancy are numerous.[16] But until recently little or no attention was paid to the direct correction of deformities of the structures underlying the skin that also become lax and contribute to the aging changes of the face and neck.

The newer face-lift operations have increasingly focused on the deeper tissues. Improved contouring of the submental and submandibular regions of the neck was advocated in the early 1970's by Millard,[17] who directly excised fat in these areas through the lateral cervical approach, combined with a separate submental incision. Connell[18] and Peterson[19] have shown that such defatting can accomplish a dramatic improvement in selected patients that cannot be achieved by a rhytidoplasty alone.

Skoog[20] in 1974 described an important aspect of the anatomy of the lower face and neck, pointing out that the skin and subcutaneous fat of the lower face and neck form a morphologic entity with the platysma muscle. These three layers are intimately connected with multiple fibrous septa. With aging, the skin, subcutaneous tissue and platysma muscle shift downward and together are responsible for the sagging appearance often shown by prominent cords of the platysma muscle in the anterior submental and neck region.

In 1976 Mitz and Peyronie[21] described the

superficial fascia of the preparotid and cheek area, which they termed the superficial musculoaponeurotic system (SMAS). With cadaver dissection they showed that the SMAS in the pretragal region is in continuity with the lateral end of the frontalis muscle in the upper part of the face and with the platysma muscle in the lower face and neck. Fibrous septa extend from the SMAS to the dermis through the subcutaneous fat, creating a wide mesh of connections between the skin of the cheek and the underlying SMAS. Mitz and Peyronie observed that surgical undermining at the superficial subcutaneous plane as is done in the classic face-lift procedure destroys these fibrous connections between the SMAS and skin. Consequently, a rhytidoplasty alone does not correct the laxity of these deeper tissues that sag with the skin.

While the SMAS and platysma are interconnected with the skin and subcutaneous tissue, the undersurface of this anatomic flap is not intimately fixed to the deeper structures. A potentially avascular space is present between the superficial flap and the external layer of the deep cervical fascia of the neck, which continues into the cheek as the true parotid fascia. Because of this anatomic configuration, the SMAS-platysma layer is easily separated from the deep cervical fascia. Almost no vessels cross this plane, but care is necessary when dissecting to identify and avoid damaging those major vessels and nerves that course just beneath the surface of the deep cervical fascia.

Incorporating the anatomic descriptions of Mitz and Peyronie with the technique of subplatysmal dissection originally advocated by Skoog, Owsley devised the technique of SMAS-platysma face lift in which the redundant tissue of the cheek, jaw line and neck are lifted by freeing and upward advancement of the compound flap comprising the interconnected skin and SMAS-platysma layer.[22-24]

Extensive experience with this technique in a large series of patients has shown several advantages of the SMAS-platysma face-lift operation.

- Minimal superficial undermining of the skin in the subcutaneous plane prevents the vascular compromise of the skin flaps that results from severing the superficial blood supply to the skin.
- Undermining in the avascular plane beneath the musculoaponeurotic layer reduces the number of blood vessels encountered and has decreased the occurrence of extensive ecchymosis and postoperative expanding hematoma.
- Superior lateral advancement of the SMAS-platysma-skin flap effectively tightens the submental and mandibular regions in a snug and longer lasting lift than with the skin lift alone.
- Complete transection of the platysma muscle across the base of the skin-platysma flap below the level of the cervicomental angle has improved the correction of prominent anterior neck cords. The muscle transection has prevented their early recurrence which has been a significant problem in patients who had a facial rhytidectomy.
- The skin flap in the upper cheek and temple area can be undermined widely superficially to the SMAS flap, with tension directed laterally to enhance correction of deep nasolabial folds.
- As lateral tension in the neck is created by sutures in the platysma flap, it is possible to place the postauricular incisions higher into the hairline to prevent visibility of this scar without compromising the degree of lower neck skin correction.
- There is less stretching of the skin with a more natural appearance, in contrast to the "pulled appearance" sometimes observed following a tight facial rhytidectomy.
- Healing of the skin incisions is accelerated because there is less tension and vascular embarrassment of the skin edges.

The most significant potential disadvantage of the technique is that of possible injury to the branches of the facial nerve. Analysis of 322 consecutive cases of platysma-SMAS facial rhytidectomies over a four-year period indicated that nine patients had a temporary decrease in function of the platysma muscle, characterized by diminished depressor activity of the chin.[23] This was related to dysfunction of either the cervical branch of the facial nerve or the platysma muscle due to transection.[25] The temporary deformity was minimal, however, and the patients recovered full function within three months. There were no instances of injury to the marginal mandibular, buccal or frontal branches of the facial nerve. The frequency of nerve injury with the SMAS-platysma operation is comparable to that published in other series in which the classical face-lift procedure was done.[26] The incidence of other complications, including extensive ecchymosis, expanding hematoma and skin slough in this series, was somewhat

less than reported in patients in whom the classical facial rhytidectomy was done.[27]

Six Representative Cases

CASE 1. A 43-year-old man, an optometrist, was seen with pronounced bagginess of the upper and lower eyelids due to prominence of the orbital fat pads. A blepharoplasty procedure was done that included removal of excess skin, orbicularis muscle and fat, including a prominent lateral fat pad in the upper lids. Medial, central and lateral fat pads were removed from the lower lids, followed by excision of the lax excess skin (Figure 1).

CASE 2. A 51-year-old male business executive had heaviness of the upper eyelids and baggy and wrinkled lower eyelids. A blepharoplasty was done that included removal of skin, orbicularis

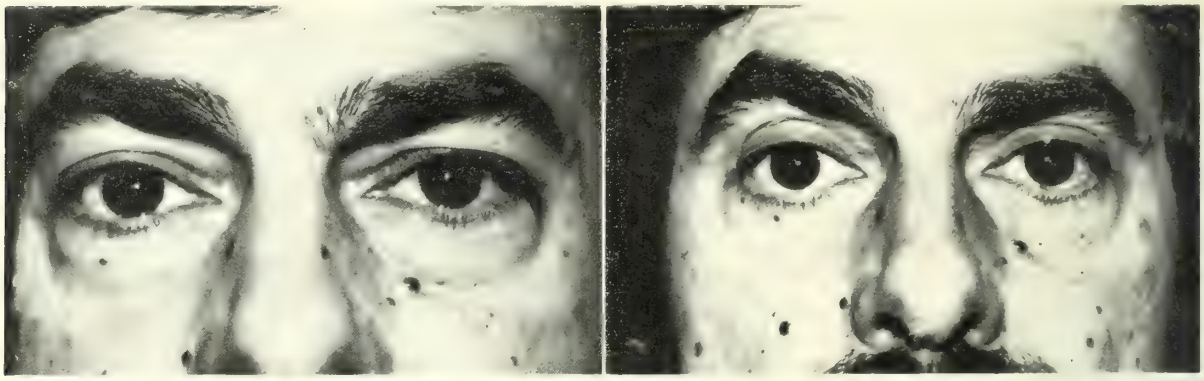

Figure 1.—Preoperative (left) and one-year postoperative (right) appearance of 43-year-old man following upper and lower blepharoplasty.

Figure 2.—Preoperative (left) and one-year postoperative (right) appearance of 51-year-old man after upper and lower blepharoplasty.

Figure 3.—Preoperative (left) and two-year postoperative (right) appearance of 41-year-old woman after upper and lower blepharoplasty.

muscle and fat pads of the upper lid. The skin of the lower lids was undermined widely from the underlying orbicularis muscle to allow redraping after excision of excess skin that followed removal of redundant fat pad (Figure 2).

CASE 3. A 41-year-old housewife had been bothered by baggy lower eyelids since her early 20's. The baggy appearance of her lower lids was typical for her family, being notable in her father and brother. A lower-lid blepharoplasty was done that included removal of prominent fat pads and excess skin of the lower lids. An upper-lid blepharoplasty was also done (Figure 3).

CASE 4. A 45-year-old female executive was seen for correction of the aging appearance of her face. Examination of her face showed laxity of the skin of the cheek and neck, with notable jowl formation and moderately prominent anterior neck cords. The upper eyelids showed folding of excess skin on the eyelashes with moderate protrusion of fat of the lower eyelids. Upper- and lower-lid blepharoplasties were done in conjunc-

Figure 4.—Preoperative (left) and one-year postoperative (right) appearance of 45-year-old woman after SMAS-platysma face lift and upper and lower blepharoplasties.

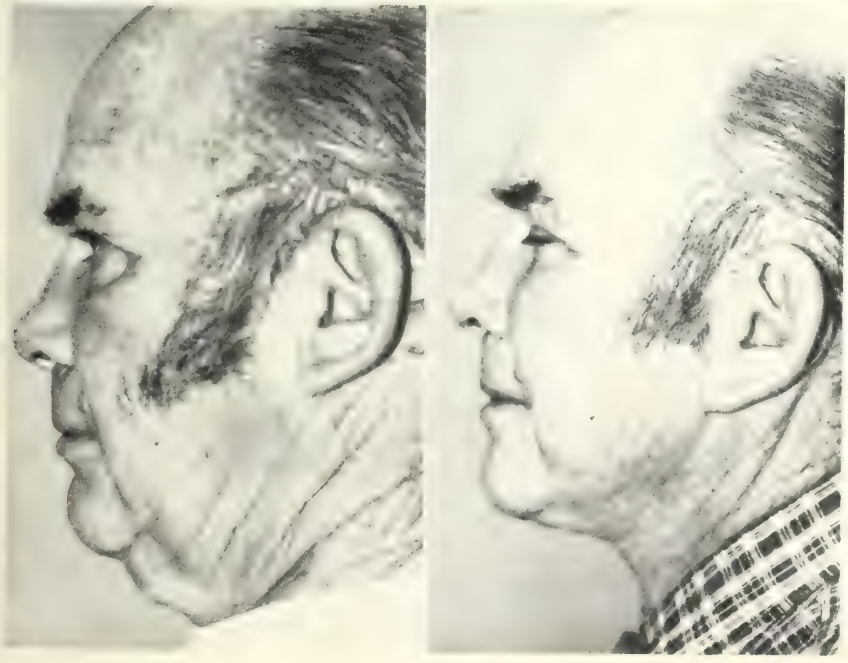

Figure 5.—Preoperative (left) and six-month postoperative (right) appearance of 71-year-old man after SMAS-platysma face lift with submental and submandibular defatting of the neck.

Figure 6.—Preoperative (left) and six-month postoperative (right) appearance of 61-year-old woman after coronal forehead brow lift, upper and lower blepharoplasties and SMAS-platysma face lift.

tion with an SMAS-platysma face lift. Neck defatting was not required (Figure 4).

CASE 5. A 71-year-old practicing dentist presented with considerable laxity of the skin of the face and neck, showing a pronounced "turkey gobbler" deformity of the anterior neck with bulky fat deposits in the submental and submandibular regions. An SMAS-platysma facial rhytidectomy in conjunction with submental and submandibular defatting of the neck was done that included an additional submental incision (Figure 5).

CASE 6. A 61-year-old housewife was seen because of the severely aged appearance of her face and neck. There was pronounced laxity and wrinkling of the skin characteristic of many years of sun exposure. The forehead showed transverse wrinkling associated with drooping brows, heavy upper eyelids and glabellar frown lines. The skin of the lower eyelids was lax and wrinkled. A one-stage surgical correction was done that included coronal forehead brow lift, upper- and lower-lid blepharoplasties and SMAS-platysma facial rhytidectomy (Figure 6).

REFERENCES

1. Berner R, Morain W, Noe J: Preoperative hypertension as an etiological factor in hematoma after rhytidectomy. Plast Reconstr Surg 57:314-319, 1976

2. Fredericks S: Panel on aesthetic facial surgery. Presented at the annual meeting of the American Society of Plastic and Reconstructive Surgeons, San Francisco, Oct 1976

3. Castanares S: Forehead wrinkles, glabellar frown and ptosis of the eyebrows. Plast Reconstr Surg 34:406-413, 1964

4. Stephenson KL: The history of face, neck, and eyelid surgery, *In* Masters FW, Lewis JP (Eds): Symposium on Aesthetic Surgery of the Face, Eyelid and Breast. St. Louis, CV Mosby Co, 1972, p 13

5. Kaye BL: The forehead lift: A useful adjunct to face lift and blepharoplasty. Plast Reconstr Surg 60:161-171, Aug 1977

6. Bames HO: Baggy eyelids. Plast Reconstr Surg 22:264-266, 1958

7. Castanares S: Blepharoplasty for herniated intraorbital fat, anatomical basis for a new approach. Plast Reconstr Surg 8:46-58, 1951

8. Baker TJ, Gordon HL, Mosienko P: Upper lid blepharoplasty. Plast Reconstr Surg 60:692-698, Nov 1977

9. Owsley JQ Jr: Blepharoplasty variations, *In* Goulian D, Courtiss EH (Eds): Symposium on Surgery of the Aging Face. St. Louis, CV Mosby Co, 1978, p 163

10. Owsley JQ Jr: Resection of the prominent lateral fat pad during upper lid blepharoplasty. Plast Reconstr Surg 65:4-9, Jan 1980

11. Owsley JQ Jr: Functional upper eyelid anatomy as applied in aesthetic blepharoplasty. Aesthetic Plast Surg 5:115-121, 1981

12. Sayoc BT: Plastic construction of the superior palpebral fold. Am J Ophthalmol 38:556-559, 1954

13. Fernandez LR: Double eyelid operation in the Oriental in Hawaii. Plast Reconstr Surg 25:257-264, 1960

14. Sheen JH: Supratarsal fixation in upper blepharoplasty. Plast Reconstr Surg 54:424-431, Oct 1974

15. Flowers RS: Bicentennial blepharoplasty. Motion picture presented at the annual meeting of the American Society of Plastic and Reconstructive Surgeons, Boston, Sep 1976

16. Rees TD, Wood-Smith D: Cosmetic Facial Surgery. Philadelphia, WB Saunders Co, 1973

17. Millard DR Jr: Submental and submandibular lipectomy in conjunction with a face lift in the male or female. Plast Reconstr Surg 49:385-391, Apr 1972

18. Connell BF: Contouring the neck in rhytidectomy by lipectomy and a muscle sling. Plast Reconstr Surg 61:376-383, Mar 1978

19. Peterson RA: The role of the platysma muscle in cervical lifts, *In* Goulian D, Courtiss EH (Eds): Symposium on Surgery of the Aging Face. St. Louis, CV Mosby Co, 1978, p 115

20. Skoog T: Plastic Surgery—New Methods and Refinements. Philadelphia, WB Saunders Co, 1974

21. Mitz V, Peyronie M: The superficial musculo-aponeurotic system (SMAS) in the parotid and cheek area. Plast Reconstr Surg 58:80-88, Jul 1976

22. Owsley JQ Jr: Platysma-fascial rhytidectomy. Plast Reconstr Surg 60: 12:843-850, Dec 1977

23. Owsley JQ Jr: Platysma-SMAS rhytidectomy, a four year experience, *In* Gradinger G, Kaye B (Eds): Symposium on Problems and Complications in Aesthetic Plastic Surgery of the Face. St. Louis, CV Mosby Co (In press)

24. Owsley JQ Jr: Discussion of Souther SG, Vistnes LM: Medial approximation of the platysma muscle in the treatment of neck deformities. Plast Reconstr Surg 67:614-615, May 1981

25. Ellenbogen R: Pseudo-paralysis of the mandibular branch of the facial nerve after platysmal face-lift operation. Plast Reconstr Surg 63:364-368, Mar 1979

26. Baker DC, Conley J: Avoiding facial nerve injuries in rhytidectomy—Anatomical variations and pitfalls. Plast Reconstr Surg 64:781-795, Dec 1979

27. Thompson DP, Ashley FL: Face-lift complications: A study of 922 cases performed in a 6-year period. Plast Reconstr Surg 61:40-49, Jan 1978

Refer to: Brenner PF: The menopause (Medical Progress). West J Med 136:211-219, Mar 1982

Medical Progress

The Menopause

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Hormone-replacement therapy for postmenopausal women has associated benefits and risks. The advantages of the administration of estrogen to postmenopausal women include preventing or reversing the atrophic changes of the genitourinary system, slowing of facial aging, relieving hot flushes and psychological symptoms, preventing atherosclerotic heart disease and retarding the development of osteoporosis. The disadvantages of the administration of estrogen to postmenopausal women include rare but serious clinical sequelae associated with the ingestion of the synthetic estrogen when it is one component of the combination oral contraceptives, increased risk of cancer developing in the estrogen-dependent organs and uterine bleeding. The benefits of long-term cyclic estrogen-gestagen therapy in preventing osteoporosis far outweigh the risks.

THE MANAGEMENT of the menopause is a medical dilemma of the 20th century. The mean age at which the menopause occurs is 51.4 years,[1] and this has not changed in the last 125 years. In the early 1900's a woman living in the United States had a life expectancy of approximately 45 years but many failed to survive beyond their reproductive years. Now a woman in this country can expect to live almost 80 years, which means that a third of her entire life span is spent in the postmenopausal years.

The term menopause most accurately refers to the age at which there is a cessation of spontaneous menstruation. It is common for both the lay public and the medical profession to use the term menopause and climacteric interchangeably in reference to the physiologic period of a woman's life during which ovarian follicles are depleted and there is a decline in ovarian function. There is a misunderstatnding by some people that the menopause can be significantly delayed if follicles are conserved during the reproductive years, either by frequent pregnancies and lactation or by the use of ovulation-suppressing hormones, the oral contraceptives. At birth the ovaries contain approximately half a million follicles, most of which are lost through atresia.[2] Only about 400 to 450 ovulations occur in the reproductive years for most women and pregnancy or the use of birth control pills do not substantially alter the time of the menopause. While the mean age of the menopause has remained the same over the last century, the mean age at menarche has been occurring progressively earlier each decade. Again, because relatively few follicles are involved compared to the initial complement of follicles at birth, the earlier age at menarche has not been accompanied by any noticeable change in the age of the menopause.

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Mechanisms of Menopause

As the ovary becomes devoid of follicles, considerable changes occur in both the sex steroids

ABBREVIATION USED IN TEXT

FSH = follicle-stimulating hormone

and the protein hormones of pituitary origin. In an ovulating woman, the secreting ovaries are responsible for virtually the entire production of estradiol and it is the predominant source of estrone.[3] A small portion of estrone is derived from the prehormone conversion of androstenedione. Estradiol is quantitatively and biologically the most important estrogen in the peripheral circulation of ovulating women. In premenopausal women one half to two thirds of the testosterone production is derived from the peripheral conversion of prehormones and the remainder is secreted by the ovaries. Androstenedione is derived half from ovarian secretion and half from adrenal secretion. A postmenopausal ovary with the absence of follicles ceases virtually all production of estrogen, but the ovarian stroma continues to secrete androgen.[4] The concentrations of estrone exceed those of estradiol in the peripheral circulation of postmenopausal women, and the source of nearly all the estrone production is the extraglandular conversion of androstenedione to estrone in the fat, liver and skin.[5,6] With advancing age and increasing weight the peripheral conversion of androstenedione to estrogen is increased.[7,8] The small amount of estradiol produced in a postmenopausal woman is derived largely from the conversion of estrone. The secretion of testosterone by postmenopausal ovaries is very similar to that of premenopausal ovaries but the secretion of androstenedione is decreased in postmenopause.[9] After menopause 85 percent of androstenedione comes from adrenal secretion and the rest from ovary. As the result of the decrease in estrogen production, the levels of estrogen in the peripheral circulation are greatly reduced, the inhibitory feedback of estrogen on the hypothalamus and pituitary is diminished and there is a rise in the levels of serum gonadotropins.

In a woman who has a hysterectomy with her ovaries left in situ before her spontaneous menopause, the determination of a serum follicle-stimulating hormone (FSH) level in the postmenopausal range is the most reliable method of diagnosing when this person becomes postmenopausal.[10] The concentrations of cortisol, prolactin, thyroid-stimulating hormone and growth hormone in the peripheral circulation of postmenopausal women is not significantly different from those levels in premenopausal ovulatory women.[11]

Indications for Estrogen Replacement

The decision to initiate hormonal therapy in a postmenopausal woman is made after careful consideration of the benefits and risks of the therapy on an individual basis. The purported advantages of the administration of estrogen to postmenopausal women are that it prevents or reverses the atrophic changes of the genitourinary system, makes women look younger, relieves hot flushes and psychological symptoms, prevents atherosclerotic heart disease and retards osteoporosis.

Atrophic Changes of the Genitourinary System

The vaginal mucosa is very sensitive to the presence or absence of estrogen. Pelvic examination of postmenopausal women deprived of estrogen will show a thin, pale, almost transparent, vaginal mucosa. The cervix may no longer protrude into the vagina and instead may be flush with the apex of the vaginal vault. In rare instances the upper third of the vagina will be narrowed or even obliterated. Women with atrophic changes of the vagina complain of vaginal dryness, pruritus, discharge and dyspareunia. They may find it impossible to attempt coitus and have a secondary effect of the loss of libido. The urethral mucosa is also an estrogen-responsive tissue. With falling levels of estrogen, the lining of the urethra becomes attenuated and a woman may experience symptoms of urinary frequency, dysuria and urgency incontinence. A low dose of estrogen given for a short interval prevents or reverses atrophy of the lower genitourinary system. Estrogen is administered either orally or as a vaginal cream. The intravaginal use of estrogen creams does not prevent the systemic effects of estrogen. The steroid rèadily crosses the vaginal mucosa and is absorbed into the peripheral circulation. The levels of estrogen in the circulation following the intravaginal administration of estrogen are as high or higher than the same amount of steroid taken orally.

Slowing of Aging

Our society places a great emphasis on its members, particularly the women, looking young. There is no evidence that the use of estrogen makes the wrinkles and lines in the skin associated

with aging disappear. It should not be used to make women look younger.

Hot Flushes

The hot flush is the most common symptom associated with the menopause. Approximately three out of every four women experience hot flushes during their transition through the perimenopause and menopause. In one out of five women the flushes persist for five years or longer. The flushes start over the upper part of the body and spread over the neck and face. They last from a few seconds up to several minutes and are more common at night, frequently waking women from their sleep.[12] They are frequently accompanied by perspiration. They occur at intervals of every 10 to 30 minutes to every week or longer. The flushes may be so bothersome that some women are unable to function satisfactorily in a vocational or social setting. The underlying endocrinopathy of the vasomotor symptoms of the menopause has been attributed to the low levels of estrogen, high circulating levels of gonadotropins, the speed with which estrogen concentrations decline in the peripheral circulation and interaction between catecholamine levels and falling estrogen levels, and increases in adrenalin, histamine and bradykinin. The latter three hormones are increased in patients with pheochromocytoma tumors who also have hot flushes. The exact cause of the hot flushes is unknown at this time. In a double-blind, randomized, crossover study women with 40 or more episodes of hot flushes each week were randomly started on either cyclic estrogen or a placebo for three months and then switched to the other regimen for three months.[13] Neither the physician nor the women knew which of them began the estrogen formulation first and which were given the placebo first. There was a significant reduction in the number of hot flushes each week in the women taking either the estrogen or the placebo first, but the relief of the hot flushes was greater with the estrogen than the placebo. The changeover from three months of cyclic estrogen therapy to three months of a placebo resulted in an increase in the number of flushes, while the change from placebo to cyclic estrogen therapy produced a further decrease in the number of flushes. These results indicate that estrogens relieve vasomotor symptoms and that there is a significant placebo effect. Psychological symptoms commonly experienced by menopausal women (irritability, anxiety, nervousness, depression, inability to concentrate, loss of memory, insomnia and fatigue) are not ameliorated by estrogens unless hot flushes are also present. As a result of the relief of the hot flushes, there are fewer periods of wakefulness at night and a secondary effect is that many of the psychological symptoms are abated.[14] A similar double-blind, randomized, cross-over study has been done recently using an oral gestagen.[15] This study indicates that the synthetic gestagen preparation reduces the number of hot flushes 75 percent and there is a 25-percent reduction by the placebo. Injectable long-acting synthetic gestagens have also been shown to be effective in relieving the vasomotor symptoms.[16,17]

Atherosclerosis

Women of all ages have a lesser incidence of heart attacks than men and the difference is even greater when women less than 40 years of age are compared with men in the same age range. Autopsy studies show that women castrated before age 40 have increased atherosclerosis compared with women who were castrated after the age of 40.[18] From these studies it has been suggested that higher concentrations of estrogen in women protect them from myocardial infarction and if their source of endogenous estrogen is eliminated at an early age, atherosclerotic changes occur. Clinically this theory has been refuted. Mortality from coronary heart disease in women increases with advancing age. At the time of the menopause the rate of this increase does not become greater. Mortality for coronary heart disease in men increases at a slower rate from middle age on and by the ninth decade approximates that in women. Women castrated before the age of 40 have the same incidence of angina, heart attacks and abnormal electrocardiograms as women who have their uterus removed but their ovaries are left in situ before reaching 40.[19] Estrogens in large doses not only did not reduce the incidence of second heart attacks in male survivors of a myocardial infarction, but actually increased the risk.[20] A recent retrospective case-control study from a large retirement community in Southern California indicated that women taking estrogen in their postmenopausal years had a significantly lower risk of death from vascular disease than those who did not take estrogen.[21] It is difficult to make a strong case in favor of administering estrogens to

postmenopausal women to prevent atherosclerotic heart disease based on one retrospective study.

Osteoporosis

Osteoporosis is a disease in which the bone mass is reduced in quantity but the remaining bone is normally calcified and normal in mineral concentration. In men and women of all ages bone is constantly undergoing the dual processes of formation and resorption. Osteoporosis may be the result of decreased bone formation, increased bone resorption or a combination of these factors. Osteoporosis in menopausal women is the result of increased bone resorption.[22] After age 40 more bone is reabsorbed than is formed. In women the rate of loss of bone mass is three times greater than in men. If sufficient bone mass is lost, fractures occur in the vertebrae and distal radius and neck of the femur, even under minimal stress.[23] Osteoporosis has been defined as being present when the bone mass falls below a critical threshold and fractures result. After age 60 years a quarter of all white women in this country have osteoporotic compression fractures of the vertebrae. By age 65 the bone mass has fallen below the threshold for fractures in half of the women in this country. After age 60 the incidence of fractures of the neck of the femur doubles each decade of life. By age 90 a fifth of all white women sustain hip fractures and, due to immobilization, emboli and fat emboli, a significant proportion of these fractures lead to death.

The determination of the calcium to creatinine ratio and the hydroxyproline to creatinine ratio in urine provides laboratory evidence that the administration of estrogen would be beneficial for postmenopausal women.[24] The administration of estrogen reverses the rise in these ratios usually seen in menopausal women who do not receive estrogen. There is clinical evidence that the administration of estrogen started within three to four years of the menopause prevents osteoporotic fractures. Serial x-ray studies of the vertebral column taken over three decades demonstrate that postmenopausal women who did not take estrogen lose as much as 5 inches of height as a result of the collapse of vertebrae that sustain osteoporotic fractures.[25] Women who begin taking estrogen close to the time of their menopause do not sustain the vertebral fractures and do not lose height.

In addition there are both retrospective and prospective case-control studies supporting the use of estrogen to prevent osteoporosis.[26,27] In one prospective study patients in a chronic-disease hospital were randomly assigned to receive either a placebo or the daily continuous ingestion of 2.5 mg of conjugated equine estrogen, with the addition of seven days of 10 mg of medroxyprogesterone acetate each month.[28] At the end of ten years the placebo group had a significant decrease in bone density while the hormonal group showed either no change in bone density if the estrogen was started more than three years following menopause or an increase in bone density if the estrogen therapy was initiated within the first three postmenopausal years. During this study seven osteoporotic fractures occurred, all in the placebo group. A much larger ongoing prospective study on the use of estrogen to prevent osteoporosis is being carried out in Scotland. The ten-year results of this investigation are now available.[29] Women who underwent surgical castration were randomly assigned to ingest estrogen or a placebo. Bone density of the third metacarpal was measured by photon absorptiometry. Women taking the estrogen had an initial slight increase in bone density and did not show a notable decrease in density over the ten years. The women assigned to the ingestion of a placebo had a significant decrease in bone density at the rate of 1.7 percent a year the first four years and then at a slower rate of 0.7 percent a year thereafter. Women who had taken estrogen for several years and then decided to stop their hormonal therapy had a rapid decrease in bone density in the next four years at a rate similar to women who never received estrogen.[30] Clinical results of this study at the end of ten years show that osteoporotic fractures developed in considerably fewer women in the estrogen-treated group as compared with the control group. The evidence shows that estrogen can be used prophylactically in postmenopausal women to prevent the occurrence of osteoporotic fractures but that it cannot be used therapeutically to substantially increase the amount of bone mass once fractures have occurred. To prevent osteoporosis, administration of estrogen should be started close to the time of the menopause, within the first three or four years, and continued long term.

In summary, estrogen-replacement therapy is indicated when there is clearly a need to reverse the atrophy of the vaginal or urethral mucosa, to relieve vasomotor symptoms and to prevent osteoporosis. Estrogen should not be administered to postmenopausal women to make them look younger, to relieve the psychological symptoms of

the menopause when they are not accompanied by hot flushes or to prevent heart attacks. Estrogen should not be held back until osteoporotic fractures have occurred in women, as the administration of estrogen will not induce an increase in new bone formation but will block a further loss of bone mass.

Risks of Estrogen Replacement

The proposed disadvantages of the administration of estrogen to postmenopausal women include the rare but serious clinical sequelae associated with the ingestion of the synthetic estrogen when it is administered as one component of the combination oral contraceptives, the increased risk of cancer in the estrogen-dependent organs and uterine bleeding.

Women taking the ovulation-suppressing hormones have been reported to be at a twofold increased risk for gallbladder disease (1 in 1,250 users per year), a threefold increased risk for deep venous thrombosis and thrombophlebitis (1 in 10,000 users per annum), a fourfold increased risk for pulmonary embolus (1 in 30,000 users per annum), a threefold increased risk for a cerebrovascular accident (1 in 30,000 users per annum), a threefold increased risk for myocardial infarction for women over 35 years of age who smoke (1 in 5,000 users per annum) and an increased risk for hypertension. Postmenopausal women taking estrogen replacement therapy have been assumed to be at the same increased risk for these serious problems and are provided a written warning to this effect when they present their prescriptions for estrogen to a pharmacist. The evidence indicates that postmenopausal women taking estrogen are at a twofold increased risk for gallbladder disease.[31] There are several studies, including those from the Boston Collaborative Drug Surveillance Program and from a retirement community in Southern California, that indicate that the administration of estrogen to postmenopausal women does not increase their chances for thromboembolic disease, stroke, myocardial infarction or hypertension.[31-35] The difference in the risk for the premenopausal woman taking birth control pills and the postmenopausal women taking estrogen therapy is most likely due to the fact that the natural estrogens used for the management of the menopause are considerably less potent than the synthetic estrogens used as a component of the combination birth control pill.[36]

Endometrial Carcinoma

Epidemiologists using retrospective case-control studies have investigated the relative risk for endometrial carcinoma in postmenopausal women taking exogenous estrogen. Estrogen replacement therapy has been reported in these studies to increase the risk for endometrial cancer 2.3- to 8.0-fold.[37-47] These studies vary greatly in the choice of control subjects, length of time of estrogen treatment, the estrogen formulations used and the histologic interpretation of the lesions reported as endometrial cancer. Criticism has been particularly strong regarding the choice of controls and the questionable accuracy of the histologic diagnosis. Despite the differences in the studies and the criticisms they have generated, they provide substantial evidence that there is a positive correlation between the administration of estrogen to postmenopausal women and the risk of endometrial carcinoma. Some but not all of the studies reported that the risk of endometrial cancer increased with duration of use and higher doses of estrogen, and the risk decreased when there was a medication-free interval each month of four or more days. The risk of endometrial carcinoma associated with exogenous estrogen administration is for those cancers with the earliest clinical stage and the lowest histologic grade; that is, stage IA, grade 1 disease. Investigators of the mechanism of action of steroid hormones indicate that estrogens increase the synthesis of both estrogen and progesterone receptors and gestagens decrease the synthesis of both estrogen and progesterone receptors. It has been proposed that the addition of a gestagen to the hormonal therapy for postmenopausal women would eliminate the mitogenic effects of the estrogen on the endometrium. Endometrial biopsy studies of British women taking estrogen with and without the addition of a gestagen tend to support this theory.[48,49] More than 40 percent of women taking continuous estrogen therapy administered by implants were found to have endometrial hyperplasia. Of women taking conjugated equine estrogen cyclically, 15 percent had endometrial hyperplasia. The addition of a gestagen for 7 days each cycle reduced the incidence of hyperplasia to 3 percent, for 10 days to 2 percent, and the addition of the gestagen for 13 or more days to the cyclic conjugated equine estrogen regimen eliminated all endometrial hyperplasia. Two studies in the United States indicate that the addition of a ges-

tagen for ten or more days to cyclic estrogen therapy given to postmenopausal women eliminates any increased risk for endometrial carcinoma and may even reduce the risk.[45,50]

Breast Cancer

The breast is known to be an estrogen-dependent tissue. There has been continual concern about an association between exogenous estrogen use and breast cancer. Ten retrospective case-control studies have addressed the issue of the relative risk of breast cancer in women receiving estrogen.[31,51-59] Not a single study has demonstrated a significantly increased risk of breast cancer in the total population. In the latest study women whose ovaries remained in situ and who ingested a total dose of estrogen in excess of 1,500 mg were at some increased risk (2.5-fold) for breast carcinoma and in another study menopausal women taking estrogen had a reduced risk (0.2-fold) the first nine years of therapy.[51,58] Three other studies of a different design failed to find an increased risk.[45,60,61] In two studies a subgroup was identified of women who were at increased risk, but there is no agreement between studies as to the makeup of this specific population.[60,61] At the present time convincing evidence is not available supporting an increased risk for breast cancer in exogenous estrogen users.

Other Complications

The one positive aspect of the menopause that women can look forward to is the cessation of menstruation. Hormonal therapy is associated with withdrawal bleeding. The older the patients and the smaller the dose of estrogen prescribed, the less likely are the postmenopausal women to bleed. Approximately a third of women ingesting the equivalent of 0.3 mg of conjugated equine estrogen, two thirds of those who receive the equivalent of 0.625 mg and over 90 percent of those who take the equivalent of 1.25 mg of conjugated equine estrogen cyclically will have withdrawal bleeding for the first three months of estrogen use. The bleeding tends to become lighter with the passage of time. Withdrawal bleeding is accepted as a physiologic response to the cyclic administration of exogenous estrogen, but breakthrough bleeding must be adequately investigated to exclude the possibility of malignant disease.[48] Cancer is not the most frequent cause of vaginal bleeding in the postmenopausal woman, but it is the most important. Uterine bleeding does hinder patient compliance. With a careful explanation prior to initiating therapy, patient dropouts due to bleeding can be kept at approximately the 5-percent level.

When electing to use a particular therapeutic modality the benefits must always be weighed against the risks. The lay press sensationalizes results expressed as risk ratio but completely abstains from presenting incidence figures. Physicians make their therapeutic decisions based on incidence and not on risk ratio. For example, if a specific risk was increased tenfold by the use of a particular drug and yet the incidence increased from 1 in 10 million to 1 in a million, a physician might still consider the use of the drug if the benefits were substantial. However, if the risk was increased twofold by the use of the particular drug and the incidence increased from 1 in 5,000 to 1 in 2,500, the physician might not use the therapeutic modality, particularly if the risk was a lethal one. The principal benefit of long-term estrogen therapy for postmenopausal women is the prevention of osteoporosis, and the principal risk is endometrial cancer. It was estimated that in 1981 700,000 new cases of osteoporotic fractures would occur in the United States and there would be 15,000 deaths attributable to osteoporosis in that year, for an incidence of 13.6 per 100,000.[62] It was similarly estimated that in 1981 38,000 new cases of endometrial cancer would occur and that there would be 3,100 deaths directly the result of this cancer, for an incidence of 2.8 per 100,000.[63] The benefits of long-term estrogen therapy for postmenopausal women far outweigh the risks.

Not all women are at equal risk for osteoporosis developing. Those at greater risk include women with a strong family history of osteoporotic fractures and women who have a small body size, fair complexion, thin skin and sparse hair. Women in this high-risk group are best advised to begin prophylactic estrogen therapy soon after their menopause. Those women at low risk for osteoporotic fractures include black women, tall women and heavy women, who have a greater bone mass to start with, and women who are committed to a daily exercise program the equivalent of walking 2.5 miles a day. Individuals in this low-risk group do not need to take estrogens to prevent osteoporosis. Most women, who do not fall into either of these groups, are best advised to use estrogen in their postmenopausal years until a

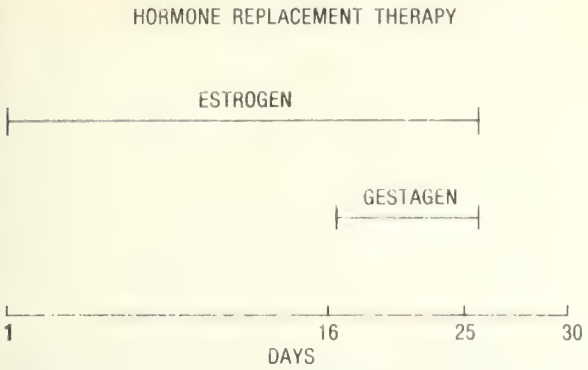

Figure 1.—The cyclic administration of hormones (estrogens and gestagens) to postmenopausal women.

marker is devised that clearly prognosticates those women in whom osteoporotic fractures will occur without estrogen therapy and those in whom they will not.

Discussion

In determining therapeutic regimens evidence favors the cyclic administration of estrogen over the continuous daily administration.[49] Evidence also strongly mandates the use of a gestagen for at least ten days each cycle. While there are no data so far to support an increase in breast cancer in women who use estrogen therapy, I advise using the same combination regimen in women who have had their uterus removed. One possible regimen for hormone-replacement therapy is the administration of estrogen the first 25 days each month and the administration of a gestagen day 16 through day 25 each month (Figure 1). Decisions still for consideration are (1) the selection of the gestagen formulation, (2) the determination of the dose of gestagen to be used, (3) the selection of the estrogen formulation, (4) the determination of the dose of estrogen to be used and (5) the route of administration.

There is very little information available concerning the choice of the gestagen formulation. In the United States C-21 acetoxy derivatives are used predominantly and in Great Britain 19-nortestosterone derivatives are used as the oral gestagens. A recent report from Sweden on the effect of orally given gestagens on lipid metabolism indicates that the 19-nortestosterone derivatives have an adverse effect on lipid metabolism, while the C-21 acetoxy derivatives do not alter lipid metabolism. There is even less information pertaining to the dose of gestagen to be used. Studies from King's College Hospital in London indicate that 1.0, 2.5, 5.0 and 10 mg of norethindrone, 150 and 500 μg of levo-norgestrel and 300 mg of progesterone all given orally reduce DNA synthesis, reduce estrogen receptors in the nucleus of endometrial cells and increase estradiol dehydrogenase activity to levels seen in the luteal phase of the menstrual cycle. Interestingly, the 1.0 and 2.5 mg dose gave better results than the higher doses of norethindrone. There is a need for more information pertaining to the selection of the gestagen formulation and the appropriate dose of gestagen.

A study comparing the estrogenic efforts of varying doses of five commonly prescribed oral estrogenic agents was recently completed at the University of Southern California Medical Center. The agents studied included conjugated equine estrogen (E_1SO_4 plus equine estrogen), piperazine estrone sulfate (E_1SO_4), micronized estradiol (E_2), diethylstilbestrol and ethinyl estradiol. The relative potency of these five estrogen formulations was determined by parallel-line analysis for the following responses: FSH suppression, an increase in corticosteroid-binding globulin-binding capacity, an increase in sex hormone-binding globulin-binding capacity and an increase in angiotensinogen. On a weight basis the synthetic estrogens were far more potent than the naturally occurring estrogens, particularly for the hepatic parameters.

At the doses now available the synthetic estrogens appear to be far too potent for use in postmenopausal women. Clinical studies and metabolic studies of the calcium to creatinine ratio in urine indicate that the equivalent of 0.625 mg of conjugated equine estrogen is necessary to prevent osteoporosis. The dose of estrogen necessary to relieve vasomotor symptoms is titrated to each patient. The cyclic estrogen-gestagen regimens are used both to relieve vasomotor symptoms and to prevent osteoporosis. When cyclic estrogen-gestagen is used in the treatment of hot flushes, every six months an attempt is made to reduce the amount of estrogen until the patient no longer requires any hormones. When estrogen-gestagen is used to prevent osteoporosis, it is continued long term.

The most common route of administration of estrogen is oral. Estrogens also can be administered by intramuscular injection, as vaginal creams, by subcutaneous implants, percutaneous application and, most recently, by a transdermal therapeutic system. The parenteral routes of administration provide an estradiol to estrone ratio

similar to the normal menstrual cycle and avoid the bolus effect, rapid metabolism and hepatic metabolic changes, seen with the oral route of administration. Many of the parenteral routes of administration may be less convenient and acceptable to the patient and they still require the addition of a gestagen and have similar effects on the endometrium as the oral ingestion of estrogen.

Conclusion

Hormone therapy consisting of the cyclic administration of an estrogen and gestagen is one facet in the management of the menopause. Other aspects of the care of postmenopausal women include encouraging them to maintain a daily exercise program and to supplement their calcium intake. All postmenopausal women are in negative-calcium balance. Changes in calcium metabolism associated with the menopause include small but significant rises in plasma calcium and phosphorus, a decreased intestinal absorption of dietary calcium, increased calcium output in the urine that is associated with an increase in the calcium to creatinine ratio in the urine and a rise in plasma alkaline phosphatase. An increase in calcium intake prevents these changes and maintains an equilibrium in calcium metabolism. Postmenopausal women require a daily intake of 1.5 grams of calcium. Their diet provides 0.4 to 0.5 grams and they require the daily supplementation of 1.0 gram of calcium. For every gram of calcium in the diet, the urinary excretion of calcium increases 60 mg and this does not increase the risk for renal calculi. Calcium is better absorbed when the stomach is empty at nighttime. The effect of estrogen and calcium on bone mass appears to be additive.

REFERENCES

1. Jaszmann LJB: Epidemiology of the climacteric syndrome, chap 2, *In* Campbell S (Ed): Management of the menopause and postmenopausal years. Lancaster, England, MTP Press, 1976, pp 11-23

2. Krouse TB: Menopausal pathology, chap 1, *In* Eskin BA (Ed): The Menopause Comprehensive Management. New York, Masson Publishing USA, 1980, pp 1-46

3. Mishell DR Jr, Nakamura RM, Crosignani PG, et al: Serum gonadotropin and steroid patterns during the normal menstrual cycle. Am J Obstet Gynecol 111:60-65, Sep 1, 1971

4. Judd HL: Hormonal dynamics associated with the menopause. Clin Obstet Gynecol 19:775-788, Dec 1976

5. Grodin JM, Siiteri PK, MacDonald PC: Source of estrogen production in postmenopausal women. J Clin Endocrinol Metab 36:207-214, Feb 1973

6. Schindler AE, Ebert A, Friedrich E: Conversion of androstenedione to estrogen by human fat tissue. J Clin Endocrinol Metab 35:627-630, Oct 4, 1972

7. Hemsell DL, Grodin JM, Brenner PF, et al: Plasma precursors of estrogen—II. Correlation of the extent of conversion of plasma androstenedione to estrone with age. J Clin Endocrinol Metab 38:476-479, Mar 1974

8. MacDonald PC, Edman CD, Hemsell DL, et al: Effect of obesity on conversion of plasma androstenedione to estrogen in postmenopausal women with and without endometrial cancer. Am J Obstet Gynecol 130:448-455, Feb 15, 1978

9. Judd HL, Judd GE, Lucas WE, et al: Endocrine function of the postmenopausal ovary: Concentration of androgens and estrogens in ovarian and peripheral vein blood. J Clin Endocrinol Metab 39:1020-1024, Dec 1974

10. Sherman BM, West JH, Korenman SG: The menopausal transition: Analysis of LH, FSH, estradiol and progesterone concentrations during menstrual cycles of older women. J Clin Endocrinol Metab 42:629-636, Apr 1976

11. Yen SSC: The biology of the menopause. J Reprod Med 18: 287-296, Jun 6, 1977

12. Mulley G, Mitchell JRA: Menopausal flushing: Does oestrogen therapy make sense? Lancet 1:1397-1398, Jun 26, 1976

13. Coope J, Thomson JM, Poller L: Effects of "natural oestrogen" replacement therapy on menopausal symptoms and blood clotting. Br Med J 4:139-143, Oct 18, 1975

14. Thomson J, Oswald I: Effect of oestrogen on the sleep, mood, and anxiety of menopausal women. Br Med J 2:1317-1319, Nov 19, 1977

15. Schiff I, Tulchinsky D, Cramer D, et al: Oral medroxyprogesterone in the treatment of postmenopausal symptoms. JAMA 244:1443-1445, Sep 26, 1980

16. Bullock JL, Massey FM, Gambrell RD: Use of medroxyprogesterone acetate to prevent menopausal symptoms. Obstet Gynecol 46:165-168, Aug 1975

17. Morrison JC, Martin DC, Blair RA, et al: The use of medroxyprogesterone acetate for relief of climacteric symptoms. Am J Obstet Gynecol 138:99-104, Sep 1, 1980

18. Parrish HM, Carr CA, Hall DG, et al: Time interval from castration in premenopausal women to development of excessive coronary atherosclerosis. Am J Obstet Gynecol 99:155-162, Sep 15, 1967

19. Ritterband AB, Jaffe IA, Densen PM, et al: Gonadal function and the development of coronary heart disease. Circulation 27:237-251, Feb 1963

20. Coronary Drug Project Research Group: The Coronary Drug Project—Findings leading to the discontinuation of the 2.5 mg/day estrogen group. JAMA 226:652-657, Nov 5, 1973

21. Ross RK, Mack TM, Paganini-Hill A, et al: Menopausal oestrogen therapy and protection from death from ischaemic heart disease. Lancet 1:858-860, Apr 18, 1981

22. Riggs BL, Jowsey J, Kelly PJ, et al: Effect of sex hormones on bone in primary osteoporosis. J Clin Invest 48:1065-1072, Jun 1969

23. Specht EE: Hip fracture, skeletal fragility, osteoporosis and hormonal deprivation in elderly women (Medical Progress). West J Med 133:297-303, Oct 1980

24. Frumar AM, Meldrum DR, Geola F, et al: Relationship of fasting urinary calcium to circulating estrogen and body weight in postmenopausal women. J Clin Endocrinol Metab 50:70-75, Jan 1980

25. Wallach S, Henneman PH: Prolonged estrogen therapy in postmenopausal women. JAMA 171:1637-1642, Nov 21, 1959

26. Hammond CB, Jelovsek FR, Lee K, et al: Effects of long-term estrogen replacement therapy—I. Metabolic effects. Am J Obstet Gynecol 133:525-536, Mar 1, 1979

27. Hutchinson TA, Polansky SM, Feinstein AR: Post-menopausal oestrogens protect against fractures of hip and distal radius—A case-control study. Lancet 2:705-709, Oct 6, 1979

28. Nachtigall LE, Nachtigall RH, Nachtigall RD, et al: Estrogen replacement therapy—I: A 10-year prospective study in the relationship to osteoporosis. Obstet Gynecol 53:277-281, Mar 1979

29. Lindsay R, MacLean A, Kraszewski A, et al: Bone response to termination of oestrogen treatment. Lancet 1:1325-1327, Jun 24, 1978

30. Lindsay R, Hart DM, Forrest C, et al: Prevention of spinal osteoporosis in oophorectomized women. Lancet 2:1151-1153, Nov 29, 1980

31. A Report From the Boston Collaborative Drug Surveillance Program, Boston University Medical Center: Surgically confirmed gallbladder disease, venous thromboembolism and breast tumors in relation to postmenopausal estrogen therapy. N Engl J Med 290:15-19, Jan 3, 1974

32. Rosenberg L, Armstrong B, Phil D, et al: Myocardial infarction and estrogen therapy in postmenopausal women. N Engl J Med 294:1256-1259, Jun 3, 1976

33. Pfeffer RI, Whipple GJ, Kurosaki TT, et al: Coronary risk and estrogen use in postmenopausal women. Am J Epidemiol 107: 479-487, Jun 1978

34. Pfeffer RI, Kurosaki TT, Charlton SK: Estrogen use and blood pressure in later life. Am J Epidemiol 110:469-478, Oct 1979

35. Pfeffer RI: Estrogen use, hypertension and stroke in postmenopausal women. J Chronic Dis 31:389-398, Jun 1978

36. Moore DE, Kawagoe S, Davajan V, et al: An in vivo system in man for quantitation of estrogenicity—II. Pharmacologic changes in binding capacity of serum corticosteroid-binding globulin induced by conjugated estrogens, mestranol, and ethinyl estradiol. Am J Obstet Gynecol 130:482-486, Feb 15, 1978

37. Smith DC, Prentice R, Thompson DJ, et al: Association of exogenous estrogen and endometrial carcinoma. N Engl J Med 293:1164-1167, Dec 4, 1975

38. Ziel HK, Finkle WD: Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 293: 1167-1170, Dec 4, 1975

39. Mack TM, Pike MC, Henderson BE, et al: Estrogens and endometrial cancer in a retirement community. N Engl J Med 294:1260-1267, Jun 3, 1976

40. McDonald TW, Annegers JF, O'Fallon WM, et al: Exogenous estrogen and endometrial carcinoma: Case-control and incidence study. Am J Obstet Gynecol 127:572-580, Mar 15, 1977

41. Gray LA, Christopherson WM, Hoover RN: Estrogens and endometrial carcinoma. Obstet Gynecol 49:385-389, Apr 1977

42. Horowitz RI, Feinstein AR: Alternative analytic methods for case-control studies of estrogens and endometrial cancer. N Engl J Med 299:1089-1094, Nov 16, 1978

43. Antunes CMF, Strolley PD, Rosenshein NB, et al: Endometrial cancer and estrogen use—Report of a large case-control study. N Engl J Med 300:9-13, Jan 4, 1979

44. Hulka BS, Fowler WC, Kaufman DG, et al: Estrogen and endometrial cancer: Cases and two control groups from North Carolina. Am J Obstet Gynecol 137:92-101, May 1, 1980

45. Hammond CB, Jelovsek FR, Lee KL, et al: Effects of long-term estrogen replacement therapy—II. Neoplasia. Am J Obstet Gynecol 133:537-547, Mar 1, 1979

46. Jelovsek FR, Hammond CB, Woodard BH, et al: Risk of exogenous estrogen therapy and endometrial cancer. Am J Obstet Gynecol 137:85-91, May 1, 1980

47. Wigle DT, Grace M, Smith ESO: Estrogen use and cancer of the uterine corpus in Alberta, Canada. Can Med Assoc J 118: 1276-1278, May 20, 1978

48. Sturdee DW, Wade-Evans T, Paterson MEL, et al: Relations between bleeding pattern, endometrial histology, and oestrogen treatment in menopausal women. Br Med J 1:1575-1577, Jun 17, 1978

49. Paterson MEL, Wade-Evans T, Sturdee DW, et al: Endometrial disease after treatment with oestrogens and progestogens in the climacteric. Br Med J 280:822-824, Mar 22, 1980

50. Gambrell RD, Massey FM, Castaneda TA, et al: Reduced incidence of endometrial cancer among postmenopausal women treated with progestogens. J Am Geriatr Soc 27:389-394, Sep 1979

51. Henderson BE, Powell D, Rosario I, et al: An epidemiologic study of breast cancer. J Natl Cancer Inst 53:609-614, Sep 1974

52. Craig TJ, Comstock GW, Geiser PB: Epidemiologic comparison of breast cancer patients with early and late onset of malignancy and general population controls. J Natl Cancer Inst 53:1577-1581, Dec 1974

53. Mack TM, Henderson BE, Gerkins VR, et al: Reserpine and breast cancer in a retirement community. N Engl J Med 292:1366-1371, Jun 26, 1975

54. Casagrande J, Gerkins VR, Henderson BE, et al: Exogenous estrogens and breast cancer in women with natural menopause. J Natl Cancer Inst 56:839-841, Apr 1976

55. Sartwell PE, Arthes FG, Tonascia JA: Exogenous hormones, reproductive history, and breast cancer. J Natl Cancer Inst 59: 1589-1592, Dec 1977

56. Wynder EL, MacCornack FA, Stellman SD: The epidemiology of breast cancer in 785 United States Caucasian women. Cancer 41:2341-2354, Jun 1978

57. Brinton LA, Williams RR, Hoover RN, et al: Breast cancer risk factors and screening program participants. J Natl Cancer Inst 62:37-43, Jan 1979

58. Ross RK, Paganini-Hill A, Gerkins VR, et al: A case-control study of menopausal estrogen therapy and breast cancer. JAMA 243:1635-1639, Apr 25, 1980

59. Jick H, Walker AM, Watkins RN, et al: Replacement estrogens and breast cancer. Am J Epidemiol 112:586-594, Nov 1980

60. Hoover R, Gray LA, Cole P, et al: Menopausal estrogens and breast cancer. N Engl J Med 295:401-405, Aug 19, 1976

61. Byrd BF, Burch JC, Vaughn WK: The impact of long-term estrogen support after hysterectomy. Ann Surg 185:574-580, May 1977

62. Hulka BS: Effect of exogenous estrogen on postmenopausal women—The epidemiologic evidence. Obstet Gynecol Surv 35: 389-399, Jun 1980

63. Silverberg E: Cancer statistics, 1981. CA 31:20-21, Feb 1981

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Malaria: A Modern Dilemma

Malaria remains endemic in large areas of the world, from many of which the United States is receiving more and more immigrants. Because of this, and rapid intercontinental travel, American physicians are likely to again encounter this relatively unfamiliar and potentially rapidly fatal disease. Accurate diagnosis and quick intervention depend upon physician awareness of the pleomorphic clinical manifestations of malaria, its laboratory identification and therapeutic approaches.

MALARIA is the most prevalent of all diseases and a scourge to men and nations throughout history. More than half a century ago Osler recognized that "No infection . . . compares with malaria in the extent of its distribution or its importance as a killing and disabling disease."[1] There are 638 million people who live where malaria is endemic and, in spite of vigorous eradication campaigns and effective prophylactic and therapeutic drugs, more than a million people die each year from this disease. Yet physicians in the United States, a sanitized sanctuary in a world of pandemic disease, often regard malaria as "one of those weird tropical diseases."

Malaria is the commonest acute febrile illness imported into the United States. The recent influx of Asian and Middle Eastern immigrants, and the danger of reestablishing endemic malaria[2] (for the mosquito vector is abundant here), make recognition and understanding of this disease by American physicians imperative. It is noteworthy that the mortality of malaria is higher in civilian victims than among miliary personnel in America. This is attributable to a greater awareness of malaria among military physicians schooled in Vietnam, and reaffirms the point that one cannot diagnose and treat a disease unless one considers it.

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Malarial Species and Cycles

Malaria is transmitted by the bite of the female *Anopheles* mosquito. The injected parasite disappears from the blood of the bitten person, usually within 30 minutes, and invades the parenchymal cells of the liver (primary exoerythrocytic cycle) where it develops for a minimum of six days. Released merozoites then enter erythrocytes and develop there by a process called schizogony. Even with multiple infections (as with multiple mosquito bites at different times) one strain of the parasite becomes dominant, somehow setting the pattern for the others such that the release of parasites from red cells and their entry into other circulating erythrocytes becomes synchronous every 48 to 72 hours. It is with this *breakout* of malarial parasites from erythrocytes that the clinical paroxysm is associated.

Merozoites may also directly reenter liver cells and remain dormant, only to reappear later, causing relapse (secondary exoerythrocytic cycle). *Plasmodium falciparum* is unique in that *all* its merozoites from liver enter erythrocytes. They do not reenter hepatic tissues as do the parasites of other species. Thus it rarely maintains clinical illness greater than one year after infection and true "relapses" do not occur.

Some of the intraerythrocytic parasites develop

into the sexual gametocytes which, when taken up by the mosquito during a blood-meal, mate in the insect and complete the cycle.

There are four malarial parasites of clinical importance to man:

- *P falciparum* is the only type that may acutely cause death in the absence of other disease. Falciparum malaria is the form of malaria that represents a medical emergency in the sense of being able to kill within 24 hours of the onset of symptoms, in its association with major complications and in its resistance to chloroquine.
- *P vivax* is the commonest malarial parasite seen in the United States. The clinical manifestations of vivax malaria are generally limited to anemia and episodes of fever.
- *P malariae,* the species causing quartan malaria, is similar in its benignity to *vivax*. However, it is remarkable in its ability to cause relapses long after exposure (perhaps as long as 30 years)[3] and the association it has with the major nonfalciparum malaria complication—the nephrotic syndrome.[4]
- *P ovale* is a West African malarial parasite and is rarely seen in the United States. Clinically, ovale malaria resembles vivax.

Most of the malaria seen in Americans returning from Southeast Asia during the Vietnam War was falciparum or vivax. Because of the shorter incubation period of falciparum (nine days from bite to symptoms, as opposed to two weeks for vivax), and because of the resistance of many strains of *falciparum* to prophylactic drugs, allowing it to become clinically manifest shortly after infection, much of *falciparum*-caused disease is diagnosed in the country of origin. Vivax malaria, on the other hand, may be suppressed by drugs until, on his return home, the traveler stops taking them. Because of this, cases of malaria diagnosed shortly after arrival in the United States may be either falciparum or vivax, whereas most patients whose clinical illness begins several weeks or months after leaving an endemic area have vivax malaria.

A great deal of emphasis has been placed in the past on species-specific diagnosis from blood smears. This is epidemiologically important, but for the clinical situation the crucial difference a physician must know is the distinction between *falciparum* and all others. Whether the parasite is *vivax* or *malariae* is not imminently critical; but one must know if it is *falciparum,* for this is truly a medical emergency. Only falciparum malaria may be acutely fatal.

Many patients will have their clinical courses modified by prophylactic drugs. Diagnosis may be made yet more complex by the fact that all kinds of malaria in the early stages may fail to show the classic asymptomatic periods; that is, synchronization of parasitic cycles may be established only after several days, obscuring the characteristic every third day (tertian) fever of vivax or falciparum malaria, or every fourth day symptoms of malariae (quartan fever). Synchronization may not occur at all during the primary attack, and daily or irregular (and thus clinically unhelpful) fever is especially common in falciparum malaria.

The only sure way of making the diagnosis of malaria and the crucial species differentiation of *falciparum* is by examination of a blood smear. If parasitemia is of a low grade, one must commit oneself to prolonged, careful examination of several blood smears taken at different times. A single negative is insufficient for exclusion of the diagnosis. Parasites may be difficult to identify with certainty on the thin smear (though they can be recognized with experience, even on a standard Wright's stained slide). For the person who sees plasmodiae only occasionally, species identification can be done from the thick smear with greater confidence. The thick smear is but a technique of concentration which involves lysis of red cells with a Giemsa stain fixative.

The smears should be examined with colored plates of typical species forms at one's side. The following generalizations are helpful to keep in mind:

- *Plasmodium vivax* infests principally reticulocytes. Schizont forms are frequent on the smear. Schüffner's dots are present in the red cells.
- *Plasmodium malariae* prefers parasitizing older cells. Like *vivax,* it shows a wide range of morphologically different intraerythrocytic stages of parasite.
- *Plasmodium falciparum,* because it invades red cells of all ages, commonly has the heaviest parasitemia (with the intensity of parasitemia directly correlating with morbidity and mortality). In this species, the examiner seldom sees any intraerythrocytic forms other than rings and gametocytes. Plentiful ameboid trophozoites or schizonts suggest another species. Most character-

istic of *falciparum* are the distinctive large, banana shaped gametocytes.

If one is uncertain of the diagnosis in a patient from Southeast Asia, it is generally wise to assume the worst and treat the patient as though he had falciparum malaria because of the frequency of chloroquine resistance and the rapidity with which severe complications may occur with falciparum.

Clinical Manifestations of Malaria

Classically, all malaria presents as recurrent paroxysms of chills and fever occurring every 36 to 72 hours. The first sign of an attack may be a dull headache or generalized malaise, shortly followed by teeth-rattling chills, cutaneous vasoconstriction and polyuria lasting an hour or less. These chills are most dramatic in *malariae*-caused disease, and may be minimal in falciparum.[5] In the transition from chills to fever, the patient may feel alternately hot and cold, then attain a high fever, with flushing, sustained for two to six hours and terminated by a drenching sweat, leaving the victim exhausted.

The classic features may be altered by the patient's prior experiences with malaria: a partially immune person's symptoms may be far less dramatic, or a first-time victim's experience a sustained or hectic, but noncyclic, fever. Headache, myalgias and a variety of gastrointestinal complaints may accompany the febrile stage of the disease. In addition to the travel history, a clinician should be alerted to the possibility of malaria in the differential diagnosis of an acute febrile illness by the occurrence, on occasion, of high morning fevers[5] and the magnitude of the temperature elevation, frequently as much as 40.6° to 41°C (105° to 106°F)—a level uncommon in other acute febrile illnesses.[6]

Though the clinical presentation of an acute malarial attack may closely resemble endotoxemia (including hypotension in falciparum malaria),[7] there is no evident passively transferrable substance in the blood of the malaria victim (other than the parasites themselves) that will reproduce the clinical syndrome in a recipient. Even the mechanism of the paroxysm, though known to correspond in time with the breakout of parasites from red cells, is unclear.[5,8]

The physical examination in malaria, other than during the paroxysm, is singularly unhelpful. Splenomegaly is variable, perhaps dependent upon the duration of subclinical illness. Only a small percentage of patients will have hepatomegaly. Jaundice is uncommon unless caused by brisk hemolysis. Malignant hyperthermia, with temperatures greater than 41.6° to 42°C (107° to 108°F) is a threat in falciparum, but is fortunately rare.[5] As mentioned, hypotension may occur in falciparum malaria even in the absence of fever, anemia or electrolyte imbalance. Patients may have sustained orthostatic drops in blood pressure that persist as long as two weeks into the recovery phase.[9] Total plasma volume in this condition has been measured and is normal or increased, but effective blood volume is decreased because of vasodilatation and peripheral pooling.[7] The resulting decrease in effective circulating volume may lead to compensatory fluid retention, hyponatremia and, occasionally, generalized edema.[10,11] Adrenocortical function has been studied and is normal.[12]

Complications of Malaria

Major complications of malaria, with one exception, occur exclusively in *falciparum* infections. These severe manifestations occur most frequently when there is a high degree of parasitemia.

Cerebral malaria occurs in about 2 percent of patients with acute falciparum malaria.[13] It may be manifested by changes in consciousness ranging from confusion to coma, behavioral changes, increased muscle tone, seizures, movement disorders, focal neurologic signs or transient cerebellar dysfunction.[13,14] The pathophysiology of cerebral malaria is unclear, but it has been attributed to intravascular coagulation of the blood supply of brain,[15] immune vasculomyelinopathy in which *Plasmodium falciparum* is the antigen,[16] increased "stickiness" of parasitized red cells with consequent vascular occlusion, or capillary leak with cerebral edema and sludging of blood flow which, combined with anemia, leads to cerebral anoxia.[13,17] Cerebral malaria is the most fearsome of all complications of this disease, and is present in a large number of those dying with falciparum infections.[18]

Pulmonary manifestations of falciparum malaria, either noncardiogenic pulmonary edema or severe intraalveolar hemorrhage, may dominate the clinical features. One of ten patients with ordinary malarial infections may have respiratory symptoms—a cough, for example. In a few patients sudden and severe pulmonary edema will develop several days after the initiation of therapy.[19] Since this commonly occurs concurrently with cerebral

malaria, a neurogenic cause may be operative. Other possibilities include increased capillary permeability, sludging of parasitized erythrocytes with capillary occlusion or consumption coagulopathy.[19,20] Progressive, refractory hypoxemia, diffuse infiltrates on x-ray films of the chest and pathologic findings of pulmonary edema, scattered hemorrhage and alveolar septal thickening make this complication most resemble an adult respiratory distress syndrome, or shock lung.[18]

Acute renal failure is one of the commonest major complications of falciparum malaria. *Blackwater* fever describes a massive, severe hemoglobinuria from abrupt hemolysis. Though it may be associated with acute renal shutdown, this hemoglobinuria need not necessarily impair renal function.[21] Formerly thought to be related to antimalarial therapy, several cases of blackwater fever have been documented in untreated patients.[22,23] And renal failure may clearly occur in the absence of blackwater fever.[24] Renal compromise may range from proteinuria[25] to oliguric acute renal failure.[26] The pathogenesis of the renal failure is probably similar to that of the acute tubular necrosis of other major medical and surgical stresses,[26,27] though intravascular coagulation has also been held responsible.[15] Predisposing features to renal shutdown appear to be severe hemolysis, intense parasitemia, and delay in adequate diagnosis and antimalarial therapy.[28] Early dialysis is generally required because of the severe catabolic state of many of these patients.[21]

The single major nonfalciparum complication of malaria also involves the kidneys, and is the nephrotic syndrome which occurs in chronic *Plasmodium malariae* infections.[4] On biopsy, histopathologic changes have ranged from diffuse or focal glomerulonephritis to patchy membranous change.[8] Immunocomplex disease, with *Plasmodium malariae* as the antigen, is probable.

The liver is almost universally involved in malaria. Even in *falciparum* infections, in which there is no secondary extraerythrocytic sequestration of the merozoites in hepatocytes, liver enzymes may be elevated and histologic abnormalities present on biopsy include Kupffer cell hyperplasia and pigmentation and periportal mononuclear cell infiltrates.[29] Malarial hepatitis is for the most part clinically inconsequential, however, and jaundice if it occurs is predominantly hemolytic.

Diarrhea may occur as part of the malarial attack, but intestinal functional abnormalities are more frequently subclinical. Studies in falciparum malaria have shown intestinal malabsorption with small bowel edema and vascular congestion.[30]

Spontaneous rupture of a chronically enlarged spleen is very rare. Though uncommon, spontaneous splenic rupture in a primary attack of acute malaria may be life-threatening.[3,31]

The Hematologic Sequelae of Malaria

Hemolysis characterizes all types of malaria, but because *vivax* prefers young erythrocytes and *malariae* old ones, only falciparum malaria—with its nondiscriminative parasitization of red cells of any age—has been associated with massive hemolysis. Anemia is not a constant finding in malaria, but is directly related to the intensity of the parasitemia. Yet the precise mechanism of anemia in malaria is a mystery. It is easy to conceive as a simple mechanical disruption of red cells by the parasites, yet both parasitized and unparasitized cells are destroyed at an accelerated rate, and uninfected as well as parasitized red cells are removed from circulation by the reticuloendothelial system.[21] Phagocytosis of erythrocytes by the reticuloendothelial system rather than mechanical intravascular hemolysis may be a major factor in the anemia of malaria.

Both parasitized and unparasitized cells in infected patients show increased osmotic fragility[32] and abnormalities of intraerythrocytic sodium and potassium concentrations suggest that red cells from infected animals may have an altered cation permeability that predisposes to their destruction.[33,34] One set of labeling experiments suggests that the spleen may actually remove parasites from infected red cells and then return these damaged but unparasitized cells to the circulation.[35] These altered cells may be the "unparasitized" cells in which abnormalities are found, and this concept would provide an explanation for the adverse effect of splenectomy in malaria as well as for the presence of spherocytes in malarious animals with intact spleens.

It has also been proposed that the metabolic demands of intraerythrocytic parasites may, by causing changes in membrane and in sodium-potassium balance, decrease the red cells' capacity to maintain normal surface negative charge. This would lead to increased aggregation and sludging of red cells in the microcirculation, accounting for the vaso-occlusive complications of the heavily parasitized host.[35]

Occasional Coombs' positivity in patients with

malaria[36] has led to the speculation that autoimmunity plays a role in hemolysis.[37]

Marrow production of erythrocytes is also impaired in malaria. Ferrokinetic studies and examination of bone marrow in victims of malaria suggest two mechanisms—one in acute and one in more chronic malaria. During an acute primary parasitemia there is a general depression of erythropoiesis. In chronic malaria, however, there may be an increase in erythroid elements in marrow, suggesting either a retardation of red cell maturation or impaired release.[38]

All these changes are quite independent of the hemolytic responses to certain antimalarials in glucose-6-phosphate dehydrogenase deficient persons.

Thrombocytopenia is common in malaria.[21] In conjunction with depletion of a broad spectrum of coagulation factors, it has been attributed by some investigators to a disseminated intravascular coagulation in falciparum malaria.[39] Others have argued persuasively for an immune-mediated thrombocytopenia.[21]

Diagnosis of Malaria

The diagnosis of malaria should be considered in any febrile patient who has been in or through an endemic area. Most contemporary victims are infected in Africa, Central and South America, India, Haiti, the Dominican Republic and Southeast Asia.[40] Others at risk include drug addicts,[41] in whom modified symptoms of malaria—chills, tremulousness, fevers, aches and pains—may be interpreted as drug withdrawal. In this case, the parasite is transmitted by shared needles. The transmission of malaria by transfusions of blood is well documented.[42,43] Transfusion-induced malaria may present with a prolonged incubation phase and atypical symptoms. The donor of the infected blood may be totally asymptomatic and surprisingly removed in time from the period of last exposure.[44] Even with modern component transfusions, malaria remains a risk; it has been reported to complicate leukocyte transfusion.[45] Malarial parasites have been described within human platelets,[46] suggesting yet another possible source of accidental infection.

Since needle or transfusion malaria transmits no hepatic merozoites, there is no exoerythrocytic phase to the illness. This makes for shorter courses of disease than in naturally acquired infections and for a different therapeutic approach.

The diagnosis of malaria is best proved by showing the presence of the parasite in the blood. Plasmodia are most readily found in capillary blood obtained by finger stick. There is no reason to await the fever spike before seeking the parasite; with falciparum malaria, in fact, parasitemia is heaviest during the afebrile periods.[5] Demonstration of the parasites may require diligent and repeated searches, and occasionally bone marrow aspiration.[47] Immunologic diagnostic techniques include indirect hemagglutination, direct immunofluorescence[48] and microhemagglutination tests.[49] These tests appear to be more useful for epidemiologic and historical surveys than for diagnosis in acutely ill patients. There is evidence that this antibody response plays a protective role in malaria,[21] giving a relative resistance to reinfection. Malaria hyperimmune globulin lowered parasitemia when given to children infected with *Plasmodium falciparum*.[50] Adults who live in areas endemic for malaria commonly have pronounced hypergammaglobulinemia which decreases when the persons are adequately treated for malaria.[50] Yet only a small amount of the total quantity of the immunoglobulin elevation in malaria seems to represent specific antibody against the parasite, and the function of most of the immunoglobulin remains obscure.[21]

Therapy of Malaria

Antimalarial drugs fall pharmacologically into four major categories[51]:

- *The quinolone derivatives,* such as quinine and chloroquine, interfere with nucleic acid replication and glucose metabolism.
- *The aminobenzoic acid (PABA) antagonists,* such as sulfonamides and dapsone, take advantage of the parasite's requirement for neosynthesis of folic acid by interfering with that synthesis.
- *Folic acid reductase inhibitors,* such as pyrimethamine and trimethoprim, work like the PABA antagonists but interfere at a different point of the folic acid synthetic pathway.
- *Other agents* are used, such as colchicine and tetracycline. First used as an antimalarial in World War II, colchicine decreases the tendency for falciparum malaria to recrudesce after quinine therapy.[52] Tetracycline, in combination with quinine, has also been used with some success in the treatment of chloroquine-resistant falciparum malaria.[53]

There are two types of cure in malaria therapy: *clinical cure* is the termination of the acute attack; *radical cure* is the eradication of the infection

itself. Clinical cure requires the use of a drug effective against circulating blood forms. Most effective for this, for all sensitive strains, is chloroquine. This agent also produces radical cure in chloroquine-sensitive falciparum malaria (which has no secondary exoerythrocytic sequestration in liver) and in transfusion or needle malaria which—no matter what the malarial species—also lacks hepatic parasites. In other types of malaria, one requires chloroquine plus a drug effective against the liver phase of the parasite. The drug of choice for this is primaquine.

Because of the high incidence of chloroquine resistance among *falciparum* from Vietnam, quinine is generally the drug of choice with this species. With severe falciparum malaria, or in any major complication of this malignant infection, parenteral administration of quinine is preferred, with transfer to orally given medication on clinical improvement. In order to prevent relapse, quinine therapy of falciparum malaria should be accompanied by therapy with pyrimethamine and a sulfa drug. Steroid therapy has been recommended as an adjunct to the specific antimalarials in cerebral malaria[13,54] and falciparum pulmonary edema.[21] Heparin therapy has been suggested to benefit patients with falciparum malaria in whom disseminated intravascular coagulation seems to be playing a role in major complications.[15,26,35] Others urge great caution in the use of anticoagulants, however.[21]

Therapies are outlined in Table 1.

Persons planning a visit to endemic malarious areas in which there are no known chloroquine-resistant strains should take 300 mg of chloroquine base weekly, beginning one or two weeks before entry to the infested region and continuing for eight weeks after return to the United States. Those who cannot avoid passing through nations in which chloroquine-resistant falciparum occurs are best advised to consult the Centers for Disease Control, Atlanta, for the most recent prophylactic recommendations. Some of those formerly used are now ineffective or (as with dapsone) shown to be potentially extremely toxic, even fatal.[55]

Conclusions

Whether malaria can be eliminated as a world disease remains to be seen. We remain obliged to continue trying, however, in this ancient battle, to develop and perpetuate mosquito elimination campaigns; to develop effective, nontoxic therapeutic agents more quickly than the parasite can develop resistance, and to remain perpetually aware, in our care of the individual febrile patient, of the possibility of this diagnosis.

REFERENCES

1. Osler W: Malaria, *In* Christian HA (Ed): Osler's Principles and Practice of Medicine, 13th Ed. New York, D. Appleton-Century Co, 1938, pp 381-394

TABLE 1.—*The Therapy of Malaria*

Species	*Therapy*	
Plasmodium falciparum (unknown sensitivity or known chloroquine resistant)	In most cases:	
	Quinine sulfate	650 mg given orally three times a day for 14 days
		plus
	Pyrimethamine	25 mg given orally two times a day for 3 days
		plus
	Sulfonamide	2 grams initially, then
		500 mg given orally every 6 hours for 5 days
	In life threatening cases (cerebral malaria, pulmonary edema, malignant hyperthermia, etc):	
	Quinine dihydrochloride	600 mg in 600 ml of normal saline solution very slowly intravenously every 8 hours
		Switch to the oral regimen outlined above *as soon as possible.*
Plasmodium vivax *Plasmodium malariae* *Plasmodium ovale*	Chloroquine base	600 mg orally immediately, after 6 hours
		300 mg orally, then
		300 mg orally daily for 2 days then
	Primaquine base	15 mg orally daily for 14 days
Plasmodium falciparum (known chloroquine sensitive) Transfusion, needle malaria (any species)	Chloroquine base	600 mg orally immediately, after 6 hours 300 mg orally, then 300 mg orally daily for 2 days

2. Stirling EL, Rowsell T: Malaria in California (Correspondence). West J Med 1981 Jun; 134:545

3. Wilcocks C, Manson-Bahr PEC: Malaria, chap 4, Manson's Tropical Diseases, 17th Ed. Baltimore, Williams & Wilkins Co, 1972, pp 39-86

4. Hendrickse RG, Glasgow EF, Adeniyi A, et al: Quartan malarial nephrotic syndrome. Lancet 1972 May 27; 1:1143-1148

5. Barrett-Connor E: Malaria. Calif Med 1971 Aug; 115:19-24

6. Deller JJ: Malaria—Again a diagnostic consideration. J Acad Fam Prac 1972 Feb; 5:68-73

7. Sonnenwirth AC, Keating JP, Waltman S: Malaria (1969). JAMA 1969 Aug 4; 209:687-692

8. Neva FA: Malaria—Recent progress and problems. N Engl J Med 1967 Dec 7; 277:1241-1252

9. Blount RE Jr: Acute falciparum malaria. Ann Intern Med 1969 Jan; 70:142-147

10. Brooks MH, Malloy JP, Bartelloni PJ, et al: Pathophysiology of acute falciparum malaria: I. Correlation of clinical and biochemical abnormalities. Am J Med 1967 Nov; 43:735-744

11. Malloy JP, Brooks MH, Barry KG: Pathophysiology of acute falciparum malaria: II. Fluid compartmentalization. Am J Med 1967 Nov; 43:745-750

12. Brooks MH, Barry KG, Cirksena WJ, et al: Pituitary-adrenal function in acute falciparum malaria. Am J Trop Med Hyg 1969 Nov; 18:872-877

13. Daroff RB, Deller JJ, Kash AJ, et al: Cerebral malaria. JAMA 1967 Nov 20; 202:679-682

14. Chipman M, Cadigan FC, Benjapongse W: Involvement of the nervous system in malaria in Thailand. Trop Geogr Med 1967; 19:8-14

15. Jaroonvesama N: Intravascular coagulation in falciparum malaria. Lancet 1972 Jan 29; 1:221-223

16. Toro G, Roman G: Cerebral malaria. Arch Neurol 1978 May; 35:271-275

17. Maegraith B: Complications of falciparum malaria. Bull NY Acad Med 1969 Oct; 45:1061-1064

18. Heineman HS: The clinical syndrome of malaria in the United States. Arch Intern Med 1972 Apr; 129:607-616

19. Brooks MH, Kiel FK, Sheehy TW, et al: Acute pulmonary edema in falciparum malaria. N Engl J Med 1968 Oct 3; 279:732-737

20. Fletcher JR, Butler T, Kopriva CJ, et al: Acute *Plasmodium falciparum* malaria. Arch Intern Med 1972 Apr; 129:617-619

21. Neva FA, Sheagren JN, Shulman NR, et al: Malaria: Host-defense mechanisms and complications. Ann Intern Med 1970 Aug; 73:295-306

22. Inman M, Hano J, Gilliland P, et al: The clinical spectrum of blackwater fever. Clin Res 1967 Apr; 15:307

23. Dukes DC, Sealey BJ, Forbes JI: Oliguric renal failure in blackwater fever. Am J Med 1968 Dec; 45:899-903

24. Sheehy TW, Reba RC: Complications of falciparum malaria and their treatment. Ann Intern Med 1967 Apr; 66:807-809

25. Berger M, Birch LM, Conte NF: The nephrotic syndrome secondary to acute glomerulonephritis during falciparum malaria. Ann Intern Med 1967 Dec; 67:1163-1171

26. Stone WJ, Hanchett JE, Knepshield JH: Acute renal insufficiency due to falciparum malaria. Arch Intern Med 1972 Apr; 129:620-628

27. Maegraith BG, Findlay GM: Oliguria in blackwater fever. Lancet 1944 Sep 23; 2:403-404

28. Sheehy TW: Disseminated intravascular coagulation and severe falciparum malaria. Lancet 1975 Mar 1; 1:516

29. Deller JJ Jr, Cifarelli PS, Berque S, et al: Malaria hepatitis. Milit Med 1967 Aug; 132:614-620

30. Olsson RA, Johnston EH: Histopathologic changes and small bowel absorption in falciparum malaria. Am J Trop Med Hyg 1969 May; 18:355-359

31. DeSaram GSW, Townsend RF: Spontaneous rupture of the spleen in malignant tertian malaria. Lancet 1943 May 8; 1:584-585

32. George JN, Wicker DJ, Fogel BJ, et al: Erythrocyte abnormalities in experimental malaria. Proc Soc Exper Biol Med 1967 Apr; 124:1086-1090

33. Overman RR: Reversible cellular permeability alterations in disease—In vivo studies on sodium, potassium and chloride concentrations in erythrocytes of the malarious monkey. Am J Physiol 1948 Jan; 152:113-121

34. Dunn MJ: Alterations of red cell sodium transport during malarial infection. J Clin Invest 1969 Apr; 48:674-684

35. Conrad ME: Pathophysiology of malaria—Hematologic observations in human and animal studies. Ann Intern Med 1969 Jan; 70:134-141

36. Adner MM, Alstatt LB, Conrad ME: Coombs'-positive hemolytic disease in malaria. Ann Intern Med 1968 Jan; 68:33-38

37. Zuckerman A: Recent studies on factors involved in malarial anemia. Milit Med 1966 Sep; 131(Suppl):1201-1216

38. Srichaikul T, Makumkrong W, Poshyachinda V, et al: Ferrokinetic studies and erythropoiesis in malaria. Arch Intern Med 1969 Nov; 124:623-628

39. Dennis LH, Eichelberger JW, Inman MM, et al: Depletion of coagulation factors in drug-resistant *Plasmodium* falciparum malaria. Blood 1967 May; 29:713-721

40. Butler T, Warren KS, Mahmoud AAF: Algorithms in the diagnosis and management of exotic diseases—XIII. Malaria. J Infect Dis 1976 Jun; 133:721-726

41. Saylor LF: Induced vivax malaria among users of intravenous heroin. Calif Med 1971 Jun; 114:73-75

42. Brooks MH, Barry KG: Fatal transfusion malaria. Blood 1969 Dec; 34:806-810

43. Czapek EE, Barry DW, Gryboski JD: Malaria in an infant transmitted by transfusion. JAMA 1968 May 6; 204:549-550

44. Verdrager J: Cerebral malaria following blood transfusion. J Trop Med Hyg 1969 Jun; 72:131-133

45. Dover AS, Guinee VF: Malaria transmission by leukocyte component therapy. JAMA 1971 Sep 20; 217:1701-1702

46. Fajardo LF, Tallent C: Malarial parasites within human platelets. JAMA 1974 Aug 26; 229:1205-1207

47. Chojnacki RE, Brazinsky JH, Barrett ON Jr: Transfusion-induced falciparum malaria. N Engl J Med 1968 Oct 31; 279:984-985

48. Kagan IG, Mathews H, Sulzer AJ: The serology of malaria: Recent applications. Bull NY Acad Med 1969 Oct; 45:1027-1042

49. Rogers WA Jr, Fried JA, Kagan IG: A modified indirect microhemagglutination test for malaria. Am J Trop Med Hyg 1968 Nov; 17:804-809

50. Cohen S, McGregor IA, Carrington S: Gamma globulin and acquired immunity to human malaria. Nature (London) 1961 Nov 25; 192:733-737

51. Hunsicker LG: The pharmacology of the antimalarials. Arch Intern Med 1969 Jun; 123:645-649

52. Reba RC, Sheehy TW: Colchicine-quinine therapy for acute falciparum malaria acquired in Vietnam. JAMA 1967 Aug 14; 201:553-554

53. Colwell EJ, Hickman RL, Kosakal S: Tetracycline treatment of chloroquine-resistant falciparum malaria in Thailand. JAMA 1972 May 1; 220:684-686

54. Woodruff AW, Dickinson CJ: Use of dexamethasone in cerebral malaria. Br Med J 1968 Jul 6; 3:31-32

55. Barrett-Connor E: Chemoprophylaxis of malaria for travelers. Ann Intern Med 1974 Aug; 81:219-224

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Advances in Interferon Research

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. NAUGHTON:* *This Medical Staff Conference is devoted to recent developments in interferon research. We are very fortunate to have with us Dr. Thomas Merigan and Dr. Abla Creasey from the Division of Infectious Diseases at Stanford University. Their work in this most exciting field has received international recognition.*

DR. CREASEY:† Interferon (IFN) is a glycoprotein produced by most animal cells on induction with viruses, double-stranded RNA and other compounds, such as polynucleotides, mitogens and polycarboxylates. IFN produces an antiviral state in cells through a process or processes that require new cellular RNA and protein synthesis. More recently, IFN has been found to express a number of biologic activities, including the following: (1) immunomodulation, (2) inhibition of cellular proliferation, (3) inhibition or enhancement of cell differentiation, or both, (4) alteration of cell surfaces and (5) enhancement of some cell functions. The expression of one or all of these biologic activities of IFN, whether in vivo or in vitro, is time-, dose- and cell-dependent. The object of this review is to summarize recent advances in the interferon field, taking into account IFN types and their identified biologic activities.

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Biochemical and Biophysical Characteristics

Three types of IFN with distinguishing characteristics have been identified (Table 1). Leukocyte or α-IFN is produced by buffy-coat leukocytes primed with IFN and induced with heat-inactivated Sendai virus at high multiplicity. α-IFN consists of two components, whose molecular weights are around 15,000 and 21,000. Fibroblast or β-IFN is produced by fibroblasts stimulated with such agents as viruses and double-stranded nucleic acids; it consists of one component with a molecular weight of 20,000. Immune or γ-IFN, with a tentative molecular weight of 40,000 to 46,000,[1] is produced by T-lymphocytes in response to mitogens or to antigens to which they are sensitized. α- and β-IFN are both acid stable (that is, they are not inactivated by exposure to acid at pH 2 for 24 hours) whereas γ-IFN is acid labile.

Originally, IFN was shown to exert less activity on heterologous cells and to have a predilection for cells of the animal producing it. However, this has been proved to be not entirely true. Human leukocyte IFN is now known to be active in bovine, porcine, feline and rabbit cells; human fibroblast IFN is active in pig cells.[1] It remains true, however, that the most consistent biologic activity exerted by a given IFN is on cells of its own species.

It has been consistently shown that antibodies raised against one IFN only neutralize the biologic

ABBREVIATIONS USED IN TEXT

CAH = chronic active hepatitis
CPA = chronic persistent hepatitis
DNAP = DNA polymerase
HBcAg = hepatitis B core antigen
HBeAg = hepatitis B e antigen
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
IFN = interferon
SGOT = serum aspartate aminotransferase, formerly serum glutamic oxaloacetic transaminase

activity of that specific IFN, with very little cross reactivity.[2] Recent findings regarding the structure and sequence of IFN (discussed later) may help explain this observation.

Recent advances in the production and purification of IFN have led to revolutionary progress in understanding the molecular structure of human IFN. Nucleotide and amino acid sequences of both leukocyte and fibroblast IFN have been identified.[3,4] As a result of determining sequences of the first 13 amino terminal amino acids of fibroblast and leukocyte IFN, it has been shown that these two IFN types differ profoundly in the primary structure of the polypeptide chain. More recently, however, a comparison between the nucleotide sequences of cloned leukocyte and fibroblast IFNs has confirmed the structural differences between the α- and the β-IFN and revealed distinct homologies. Weissmann and his colleagues[5] found that human leukocyte IFN and human fibroblast IFN show homologies of 45 percent at the nucleotide level and 29 percent at the amino acid level, principally within two domains of the molecule. Such an observation suggests that two different genes code for the two IFNs and that the two genes were derived from a common ancestry a few million years ago. More recent findings in the cloning of IFN suggest the existence of multiple genes, that is, eight or more α-IFN genes in the human system, because several distinct human chromosomal DNA fragments cross-hybridized with the complementary DNA (cDNA) of the α-IFN that was cloned in *Escherichia coli*.[6]

Production

Much effort in the past two years has been directed toward large-scale production of IFN because of its clinical potential as an antiviral and antitumor agent. Previous production methods mainly involved tissue culture.[1] More recently, however, recombinant DNA techniques have succeeded in producing cloned homogeneous IFN of both the α and the β types. Table 2 is a schematic of the basis of that technology.

Two main strategies have been used to produce the IFN messenger RNA (mRNA)-cDNA molecule that has been integrated into a plasmid. One strategy involved the isolation and purification of the IFN mRNA from cells that have been primed and superinduced to make IFN.[7] A double-stranded cDNA was synthesized from this purified message by using reverse transcriptase and polymerase-1. The complementary DNA is then hybridized with a specific plasmid.

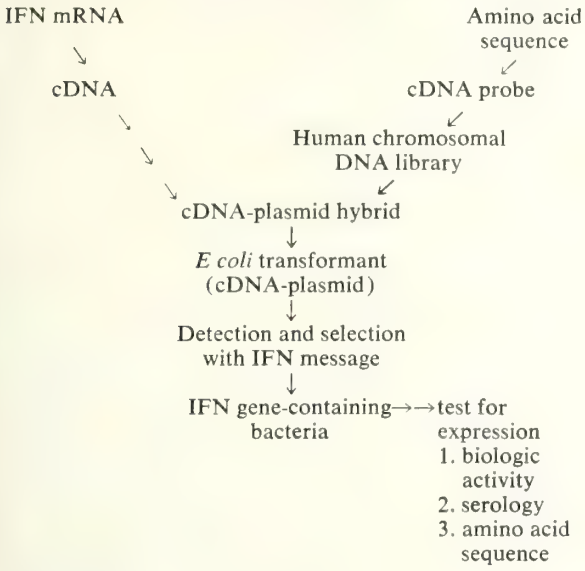
The other strategy began with a partial amino acid sequence of IFN from which a synthetic cDNA probe was prepared. That probe was then used to locate regions in a human chromosomal DNA restriction endonuclease fragment library that would hybridize with the IFN cDNA sequences.[8] The double-stranded DNA picked out of the human chromosomal library is then the source of the complementary DNA for integration into a plasmid. For either strategy, once complementary DNA plasmid hybrids are made, they are used to transform the bacteria, *E coli,* and a number of transformants are usually generated. Bacterial colonies containing hybrid plasmid DNA are selected on agar plates containing an antibiotic, such as ampicillin, the resistance to which is transferred by the plasmid. The antibiotic-resistant colonies are then screened for their content of interferon genes by

TABLE 1.—*Defining Characteristics of Human Interferon*

Type of IFN	*Acid Stability*	*Molecular Weight*	*Host Range*	*Serology*	*Structure*
Leukocyte (α-1 through 9)	+	15,000 & 21,000 (2 components)	Bovine, porcine, feline and rabbit	Neutralized by anti-α	Show homologies of 45% at the nucleotide and 29% at the amino acid levels; principally within 2 domains: α-1 through 9 have 85-99% identity.
Fibroblast (β)	+	20,000	Rat, rabbit	Neutralized by anti-β	
Immune IFN (γ)	−	40-46,000	Pig	Neutralized by anti-γ only	ND

ND = no data.

TABLE 2.—*Interferon Production by DNA-Recombination Techniques*



IFN = interferon

in situ colony hybridization.[9] Briefly, this procedure involves spotting the bacterial colonies on nitrocellulose filters, denaturing and fixing their DNA to the filters in situ. The resulting DNA extracts of the colonies are then hybridized to a radioactive RNA that defines the sequence or gene of interest.

The interferon-producing bacteria are selected and tests for expression of the gene are then conducted. Three main methods have been used to check for the expression of the interferon gene: (1) continuously monitor for the biologic activity of the messenger RNA or the generated product by their translation and expression in frog oocytes and then by the plaque-reduction assay of the translated message, (2) use anti-interferon antisera to identify and quantitate the product and (3) analyze the nucleotide sequence of the product being made by the transformants and compare it with a known interferon nucleotide sequence.

Recently, purified high-specific activity α-2 interferon, as produced by the recombinant DNA technology, has been made available for clinical investigation.

Biologic Functions

Antiviral Activity

Interferon inhibits the transcription or the translation (or both) of a number of RNA and DNA viruses.[1] For example, IFN inhibits the transcription of vesicular stomatitis viral messages and inhibits the translation of encephalomyocarditis viral proteins. In the case of the oncogenic simian virus 40, IFN affects its replication in varied degrees and in a number of ways, including inhibition of its uncoating step and inhibition of the transcription of its T-antigen under certain conditions.[10,11] Murine leukemia viruses are affected rather differently. They are not released from IFN-treated, virally infected cells, and those released have high particle-to-infectivity ratios.[12]

A study of the role of interferon in the pathogenesis of viral diseases in animals has elegantly shown the importance of this substance against viruses. Using antisera directed against IFN, the pathogenesis of encephalomyocarditis virus and other viruses was greatly altered in that tissues not normally affected by these viruses were involved and fatalities were accelerated.[13,14] In humans, on the other hand, IFN treatment of hepatitis B patients (as will be discussed later) decreased the number of circulating Dane particles,[15] and in herpes zoster patients early IFN treatment inhibited dissemination.[16]

Immunomodulation

Interferon has several effects on the immune system. With respect to humoral immunity, IFN inhibits the primary responses of primed spleen cells to both T-dependent and T-independent antigens in vitro,[17] and it also inhibits the primary and secondary responses to T-dependent antigens such as sheep erythrocytes. Interferon effects in vivo are both time- and dose-dependent[18,19]; if interferon is given 4 to 48 hours before the antigen, maximum suppression of the antibody response is achieved. However, if interferon is given 48 to 72 hours after the antigen, the antibody response is enhanced. Interferon was also found to enhance the generation of antibody-forming cells,[20] but the mechanism for this is not well understood. IFN affects not only humoral immunity, but cellular immunity also. Interferon inhibits the sensitization of mice to contact allergens and inhibits the delayed hypersensitivity response to those allergens.[21,22] IFN enhances the cytotoxic activity of sensitized lymphocytes, phagocytic activity of macrophages and the number and activity of natural killer cells.[23-25] IFN also inhibits graft vs host reaction and prolongs allograft survival.[26]

Anticellular Action

Interferon inhibits the growth of transplanted tumors in mice.[27] IFN also inhibits the regenera-

tion of liver in partially hepatectomized mice.[28] High doses of IFN, that is, 800,000 U per ml, were also found to inhibit and retard the growth and development of suckling mice, while low doses of IFN prolonged their life span.[29] This observation is now known to be related to the presence of lymphocytic choriomeningitis virus infection in the mice.[30]

In humans, IFN has a tumor-reducing effect in various lymphomas, myelomas and some breast carcinomas.[31,32]

Inhibition of growth of tumor as well as normal cells by IFN is seen in vitro.[33-37] In most cases, however, IFN units severalfold higher are needed to inhibit the replication of normal cells as compared with the tumor cells. Interferon inhibits the replication of both virally induced and nonvirally caused tumor cells.[1,38] In general, IFN is not cytotoxic and the inhibition of growth is reversible, depending on the length of exposure (A. A. Creasey, PhD, unpublished data, December 1981).

Interferon affects the rate of cell division and, depending on the conditions of growth, inhibits cell cycling. When added to growing cells, IFN impedes the progression of cells through all phases of the cell cycle but, when added to high-density serum-stimulated cells, it decreases their transition out of the quiescent phase into synthesis, prolongs the synthetic period, and eventually inhibits cell cycling.[37]

Differentiation Effects

Depending on the dose, IFN exhibits a biphasic regulatory activity on the differentiation process of cells in culture. For example, low doses of IFN (5 to 250 U per ml) enhance dimethyl sulfoxide (DMSO)-induced erythroid differentiation of Friend leukemia cells, while high doses (above 1,000 units per ml) depress that effect.[39] Similarly, melanin synthesis in human melanoma cells in culture is enhanced by treatment with low doses of interferon and is decreased or completely inhibited by high doses (A. A. Creasey, PhD, unpublished data, December 1981). This dose-dependent biologic phenomenon has also been observed in the immunomodulatory effects of IFN and may be related to a feedback mechanism that regulates IFN action.

Cell-Surface Alterations

Membrane changes have been observed in IFN-treated cells. Interferon has been reported to enhance the expression of major histocompatibility complex on normal and leukemic murine cells,[40-43] to alter cellular morphology (that is, epithelial cells become elongated and bipolar similar to fibroblasts),[44] to increase the net negative charge on cells as measured by cell electrophoresis,[45] to enhance the expression of mitogen receptors as measured by an increase in binding of radioactive concavalin A to the cell surface[46] and to inhibit or slow down the transport of some nucleotides such as thymidine into cells.[47] It remains unclear, however, as to whether the aforementioned cell-surface changes caused by IFN treatment are specific or nonspecific. Evidence is now turning more toward specificity rather than random alteration of the cell membrane. For example, an enhancement of only certain domains within the histocompatibility locus argues against random changes.[48]

TABLE 3.—*Early Events in Interferon Action*

Events	*Time*
Rapid binding of interferon	0 hr
Interaction with specific receptor	
(a) membrane changes	1 hr
(b) possible internalization of interferon	
Nuclear response (transcription)	2 hr
Interferon-induced enzymes start to accumulate (translation)	3 hr
	12 hr

Other biologic functions enhanced by interferon include production of some cellular enzymes such as aryl hydrocarbon hydroxylase,[49] susceptibility of cells to toxicity of double-stranded nucleic acids,[1] resistance to toxins[50] and IgE-mediated histamine release from basophils.[51]

Although most of the nonantiviral activities of interferon were shown using crude, partially purified interferon, the use of electrophoretically pure mouse interferon has confirmed nearly all these effects,[52] negating the idea that the biologic effects can be ascribed to contaminants of the IFN preparation.

There is no one mechanism as yet to explain the common basis for the varied biologic activities exhibited by interferon. In fact, the only mechanism of action of interferon that is well described to date is that of its antiviral activity.

Mechanism of Antiviral Action

The sequence of events known to occur on interferon treatment is outlined in Table 3. This

schematic view of early events in interferon action is based on experimental evidence gathered by a number of laboratories as summarized by Revel and co-workers.[53] Interferon is thought to bind to cells; specifically, it has been shown to bind to gangliosides.[54,55] Interaction of interferon with a specific receptor is also suspected because of the findings that interferon binding to a surface component is coded by chromosome 21 and that antibodies directed against interferon or the surface component, that is, the receptor, inhibit this binding.[56] Intracellular nuclear response is thought to start at around two hours following interferon treatment. At this stage, the antiviral state of enzyme induction becomes actinomycin-D (dactinomycin) resistant. Interferon-induced enzymes start to accumulate between 3 and 12 hours. This is deduced from the fact that actinomycin D at this step superinduces the antiviral state and the specific enzymes induced by interferon in cells begin accumulating. Table 4[53,57,58] shows that three enzymes are known to be induced in interferon-treated cells, each of which is involved in the regulation of protein synthesis (a protein kinase, a 2′-5′-oligoisoadenylate synthetase and a phosphodiesterase). The induction of the three enzymes and response to interferon correlates well with inhibition of viral replication in a number of cells.[53,57] Double-stranded RNA and adenosine triphosphate (ATP) are required for the activation of these enzymes, which ultimately leads to the inhibition of translation of the viral message.

The preferential degradation of viral messenger RNA as compared with the host messenger RNA in the interferon-treated cell is of great interest. A satisfactory explanation for this has not yet been found. However, hypotheses and models have been proposed, a couple of which suggest the following: (1) In the case of the 2′-5′-oligoisoadenylate, the activated endonuclease preferentially degrades messenger RNA linked to double-stranded RNA.[59] Therefore, in infected cells, localized activation of the endonuclease takes place near the replicative intermediates of RNA viruses, resulting in the degradation of mainly the viral message. (2) In infected cells, there is more viral message than cellular message, which is why endonuclease activation will degrade more of the viral message and less of the cellular message—simply because there is more of it.

It seems reasonable to expect to relate the antiviral activity and the cytostatic action of interferon through one mechanism, that is, mainly through the three enzyme systems mentioned above. Recently the 2′-5′-oligoisoadenylate has been introduced into normal and tumor cells. Its biologic action seems to mimic that of interferon, as it inhibits both protein and DNA synthesis in cells.[53] In general, levels of the oligonucleotide and the kinase are enhanced in interferon-treated cells. The importance of this increase in the cytostatic action of IFN remains to be shown.

Clinical Uses of Human Interferon

DR. MERIGAN:* We will review our progress in the use of human interferon as a therapeutic agent for human viral disease and certain malignancies. For purposes of this discussion, interferon is to be thought of as a lymphokine. As a result of recombinant DNA technology, it is now the most well-characterized and most readily available member of this group of biologically active substances. Hence, with the current availability of interferon from this source and from buffy coat leukocytes and mass cultures of transformed hu-

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TABLE 4.—*Interferon-Induced Translation Regulation*

	Pathway 1	*Pathway 2*	*Pathway 3*
Enzyme induced:	Protein kinase (PKi)	Oligoisoadenylate synthetase	Phosphodiesterase
	↓	↓	↓
	activated (PKi)	oligoisoadenylate (2′-5′ pppApApA)	
	↓	↓	↓
	phosphorylation of eIF-2	activation of endonuclease	removal of CCA terminus of tRNA
Effect:	Inhibition of peptide-chain initiation	Degradation of mRNA and polysomes	Inhibition of polypeptide-chain elongation

Abbreviations: CCA = terminal nucleotide triplet in transfer RNA; eIF-2 = equals initiation factor 2; mRNA = messenger RNA; tRNA = tranfer RNA.

man B lymphocytes (lymphoblastoid cells), its pharmacologic status is the most advanced. Much more clinical work needs to be done, however.

The public information media have given much attention to interferon in recent years. Unfortunately, the potential of its broad spectrum of action on viruses and tumor cells has been stressed regardless of our very limited knowledge of its scope of efficacy. In addition, there has been no discussion of its pharmacologic limitations. For example, it has definite side effects, albeit reversible in most situations, and its high molecular weight limits its distribution even after intravenous administration. The antiviral and antitumor agent areas are rapidly growing. With the current activity, it is difficult to accurately assess an important role for any single agent.

Although there has been much interest in the clinical application of human interferon in viral infections, little material has been produced for this purpose over the years. Our group has been fortunate to have been supplied with interferon since 1972 by Dr. Kari Cantell at the State Serum Institute in Helsinki, Finland.[60]

Interferons and Varicella-Zoster Infections

The effect of human leukocyte interferon on localized herpes zoster infections was tested in three randomized placebo-controlled double-blind trials involving 90 patients with various forms of cancer.[16] Higher doses of more purified interferon in the second and third trials produced a significant ($P<.01$) decrease in cutaneous dissemination. No dissemination occurred in those receiving the highest dosage (5.1×1 million U per kg per day) ($P<.025$). The number of days of new vesicle formation in the primary dermatome decreased in this group (mean 2.2 days, $P<.05$). Treated patients had a trend toward less acute pain and significantly ($P<.05$) diminished severity of postherpetic neuralgia at the two highest dosage levels. Visceral complications were six times less frequent in interferon recipients. High-dose interferon thus appeared effective in limiting cutaneous dissemination, visceral complications and progression within the primary dermatome.

The design of the localized herpes zoster trials involved early administration of human leukocyte interferon with between 1 and 10 million units per mg protein for five to seven days or, in other words, the full period during which patients are at risk for visceral complications. In the second and third trials, patients were started on treatment at an average of two days after onset of the rash in the primary dermatome.

More recently, we have analyzed the results of a fourth placebo-controlled randomized double-blind trial in the same population involving only 48 hours of therapy at the dosage used in the third trial.[61] In this trial there was no effect on acute pain or disease progession in the primary dermatome. A modest but significant effect was noted in that distal cutaneous spread was diminished in the treated patients compared with controls, and the treated patients had diminished severity and duration of postherpetic neuralgia. The results of this study indicated that in addition to a high dosage, a significant duration of treatment with human leukocyte interferon is required to modify herpes zoster infections in patients with cancer.

Because of our results with herpes zoster, we have undertaken to extend this approach to primary infection by the same virus, that is, varicella, in children with cancer. Eighteen patients in whom varicella developed while they were undergoing therapy for a malignancy received human leukocyte interferon in a small randomized (placebo) controlled trial.[62] These studies were conducted with only the lower two doses used in our initial herpes zoster trial, that is, $4.0\times100{,}000$ U per kg or 2.55×1 million U per kg. The average treatment in this trial was 6.4 days. Complications of varicella occurred in six of the nine placebo recipients but were observed in only two of the interferon recipients. In addition, the interferon was tolerated without notable side effects. Because of these results, we have begun a randomized double-blind study of human leukocyte interferon prophylaxis for varicella in immunocompromised children whose exposure to the virus had not been identified until late in the incubation period when no benefit from passive antibody prophylaxis could be expected. Our other trial in varicella is ongoing and is a randomized double-blind study of human leukocyte interferon for the treatment of early varicella in immunocompromised children with cancer.

Interferon in Chronic Viral Infections

We have also attempted to treat patients with chronic viral infections, first focusing on neonates. Although high-dose leukocyte interferon transiently diminished cytomegalovirus viruria in infants, side effects were recognized.[63] Because of the decreased weight gain, transient liver-enzyme elevation and the transient nature of the antiviral

effect, these observations were not pursued further with the interferon preparations then available.

However, we have had more success in using interferon in the treatment of chronic hepatitis B infection.[15] Over the past five years, 32 patients with chronic hepatitis associated with persistent hepatitis B virus (HBV) infection have received 16 courses of human leukocyte interferon, 5 courses of adenine arabinoside and 21 courses of these two agents used in combination. The aims of this study were to follow the effects of these agents on HBV markers in serum and liver tissue, evaluate different regimens to select one with a reasonable toxicity-to-efficacy ratio that could be used in a controlled multicenter trial, and attempt to identify patients' clinical and virologic characteristics that might influence the outcome of therapy.[64]

Interferon was given as subcutaneous or intramuscular injections in dosages between 2.5 and 20 million units daily. Adenine arabinoside was given intravenously at dosages of 5 to 15 mg per kg daily. An additive effect of adenine arabinoside was observed on the suppression of viral markers induced by interferon. Interferon was shown to maintain viral markers at low or undetectable levels when prior adenine arabinoside therapy was discontinued. Combination courses of overlapping cycles of interferon and adenine arabinoside were developed. The mean treatment period ranged from four to six months.

Twenty patients with chronic active hepatitis (CAH) and 12 patients with chronic persistent hepatitis (CPH) who had been surface antigen (HBsAg)-positive for at least a year and had been shown to have stable detectable levels of HBV-associated DNA polymerase (DNAP) activity in their serum were studied. DNAP was used as the most sensitive index of ongoing viral replication. Hepatitis B e antigen (HBeAg), HBsAg titers and their respective antibodies were followed in all patients. Immunofluorescent staining of liver biopsies for HBsAg and core antigen (HBcAg) was also carried out.

Three types of responses were observed in the patients. Within 48 hours of starting interferon or adenine arabinoside there was a predictable fall in DNAP activity in all patients. In the majority of patients treated with a single agent, this effect continued only as long as therapy was maintained (Type III response). With interferon alone, 4 out of 16 patients showed a permanent fall in DNAP activity to undetectable levels and permanent loss of HBeAg (Type II response). In two of these patients serum HBsAg also became undetectable (Type I response) and in one patient's serum antibody to hepatitis B surface antigen was noted.

Of six patients treated with adenine arabinoside alone, only one patient's serum became permanently DNAP- and HBeAg-negative, while HBsAg remained detectable at low titers (Type II). Four of six females in the study had permanent responses to a single agent (three following interferon and one following adenine arabinoside). Only 1 out of 11 men responded permanently to interferon alone and none of 5 treated with adenine arabinoside alone (Type II) responded.

With multiple cycles of combined interferon and adenine arabinoside, 7 out of 16 patients became permanently DNAP- and HBeAg-negative as noted by serum. One of these patients' titers became HBsAg-negative (Type I) and there was a marked drop in HBsAg titers in the remaining six (Type II). Anti-HBe became detectable in four and anti-HBs in titers from five of these patients.

Of 69 patients who met the criteria for admission to the program, spontaneous falls in DNAP activity without treatment were observed in only 9 percent over a mean observation period of ten months. Only one patient became HBsAg-negative. Treatment with interferon therefore appears to be effective in permanently reducing HBV markers in women, whereas combination therapy with adenine arabinoside is more effective in men.

Patients with chronic active hepatitis and lower initial DNAP levels responded considerably better than other patients. There was a strong association between a successful therapy response and a rise in serum aspartate aminotransaminase (formerly serum glutamic oxaloacetic transaminase, SGOT) values during treatment (mean rise 145 ± 106 IU in Type I and II patients, compared with 40 ± 12 IU in Type III patients). The rise was more pronounced in women and in patients with CAH and was associated with a fall in DNAP activity. This rise might indicate host immune responses working in conjunction with the antiviral agents.

In the patients with Type I and II responses there was a marked improvement in symptoms following treatment. SGOT values fell significantly in these patients but there were no changes in the SGOT levels in Type III patients. All Type I and II patients have SGOT levels within twice the normal range at a mean period of 16 months after discontinuation of treatment. A return to normal values was seen in serum total bilirubin, alkaline phosphatase, albumin and globulin but statistical

significance was noted only in the total bilirubin ($P<.05$). On blind review of the liver biopsies, there was a significant reduction in inflammatory activity in the Type I and II patients compared with the Type III patients ($P<.01$).[65] There was also a change in histologic classification from CAH to CPH in five responsive patients and there were no changes in the unresponsive patients. There was also marked loss of infectivity in sera from Type I and Type II patients following treatment, as evidenced by chimpanzee infectivity studies. Inoculation of pretreatment sera from one Type I patient and six Type II patients studied led to HBV infection in seven chimpanzees at dilutions varying between 10^{-2} to 10^{-7}. Inoculation of undiluted posttreatment sera from these same patients failed to produce infection in seven other chimpanzees.[66]

Fever, general malaise and falls in neutrophil and platelet counts were the main observed side effects resulting from interferon therapy. Gastrointestinal and neurologic side effects were encountered following adenine arabinoside treatment.[67] These side effects were found to be dose-related and were also increased by concurrent administration of interferon. This finding has led to the use of these drugs consecutively rather than concurrently, that is, cycles of adenine arabinoside followed by interferon. We plan to test these observations in a prospectively controlled randomized trial. We are also in the early stages of evaluating the acute Dane particle-suppressive actions of one type of bacteria-produced α-interferon.

Interferon and Non-Hodgkin's Lymphoma

In addition to these studies in viral infections, we have studied the action of interferon in human malignancies, specifically non-Hodgkin's lymphoma. Initially we failed to show any effect from four weeks of daily high-dose interferon treatment in rapidly advancing histiocytic lymphoma that had failed to respond to other therapy. However, we did get substantial tumor shrinkage with the same regimen in three consecutive patients with nodular, poorly differentiated lymphoma,[31] which encouraged us to further expand this experience. So far we have observed one complete, three partial and three minimal responses in five of seven evaluable patients with nodular non-Hodgkin's lymphoma.[68] The duration of the response appears to be from 6 to 12 months. Interestingly, with this one-month course of therapy, one patient received a second partial response on re-treatment with interferon despite having received chemotherapy between his courses of interferon. Much further work needs to be done to determine the optimal use of human leukocyte interferon in these and other malignancies. Because of the chronic and recurrent nature of cancer and the other multiple modes of therapy available for such patients, a number of different dosage regimens of interferon alone and in combination with other therapy must be explored eventually in controlled trials. We are evaluating recombinant DNA bacteria-produced α-interferons, first in studies directed toward its pharmacokinetics and safety and, afterwards its efficacy in cancer patients.

The studies I have described thus represent an important experience with this material for a single group of investigators. Now that new sources of interferon have appeared, particularly through the use of recombinant DNA, there is a need for new investigators to enter this field. We need their imagination and skills to deal with the considerable problems remaining in exploring the clinical use of human interferon in disease.

REFERENCES

1. Stewart E II: The Interferon System, chap 7. New York, Springer Verlag, 1979, p 134

2. Havell EA, Berman B, Ogburn CA, et al: Two antigenically distinct species of human interferon. Proc Natl Acad Sci USA 72:2185-2187, Jun 1975

3. Knight E Jr, Hunkapiller MW, Korant BD, et al: Human fibroblast interferon: Amino acid analysis and amino terminal amino acid sequence. Science 207:525-526, Feb 1980

4. Zoon KC, Smith ME, Bridgen PJ, et al: Amino terminal sequence of the major component of human lymphoblastoid interferon. Science 207:527-528, Feb 1980

5. Taniguchi T, Mantei N, Schwarzstein M, et al: Human leukocyte and fibroblast interferons are structurally related. Nature 285:547-549, Jun 1980

6. Nagata S, Mantei N, Weissmann C: The structure of one of the 8 or more distinct chromosomal genes for human IFN. Nature 287:401-408, Oct 1980

7. Taniguchi T, Sakai M, Fuji KY, et al: Construction and identification of bacterial plasmid containing the human fibroblast interferon gene sequence. Proc Jpn Acad Ser B 55:464-469, 1979

8. Goeddel DV, Yelverton E, Ullrich A, et al: Human leukocyte interferon produced by E coli is biologically active. Nature 287: 411-416, Oct 1980

9. Grunstein M, Hogness D: Colony hybridization: A method for the isolation of cloned DNAs that contain a specific gene. Proc Natl Acad Sci USA 72:3961-3965, Oct 1975

10. Yamamoto K, Yamaguchi N, Oda K: Mechanism of interferon-induced inhibition of early simian virus 40 (SV_{40}) functions. Virology 68:58-70, Nov 1975

11. Oxman MN, Levin MJ: Interferon and transcription of early virus-specific RNA in cells infected with simian virus 40. Proc Natl Acad Sci USA 68:299-302, Feb 1971

12. Chang EH, Mims SJ, Triche TJ, et al: Interferon inhibits mouse leukaemia virus release: An electron microscope study. J Gen Virol 34:363-367, Feb 1977

13. Gresser I, Tovey MG, Bandu ME, et al: Role of interferon in the pathogenesis of virus diseases in mice as demonstrated by the use of anti-interferon serum—I. Rapid evolution of encephalomyocarditis virus infection. J Exp Med 144:1305-1315, Nov 1976

14. Gresser I, Tovey MG, Maury C, et al: Role of interferon in the pathogenesis of virus diseases in mice as demonstrated by the use of anti-interferon serum—II. Studies with herpes simplex, Moloney sarcoma, vesicular stomatitis, Newcastle disease, and influenza viruses. J Exp Med 144:1316-1323, Nov 1976

15. Greenberg HB, Pollard RB, Lutwick LI, et al: Effect of human leukocyte interferon on hepatitis B virus infection in patients with chronic active hepatitis. N Engl J Med 295:517-522, Sep 1976

16. Merigan TC, Rand KH, Pollard RB, et al: Human leukocyte interferon for the treatment of herpes zoster in patients with cancer. N Engl J Med 298:981-987, May 4, 1978

17. Gisler RH, Lindahl P, Gresser I: Effects of interferon on antibody synthesis in vitro. J Immunol 113:438-444, Aug 1974

18. Brodeur BR, Merigan TC: Mechanism of the suppressive effect of interferon on antibody synthesis in vivo. J Immunol 114:1323-1328, Apr 1975

19. Sonnenfeld G, Mandel AD, Merigan TC: Time and dosage dependence of immunoenhancement by murine type II interferon preparations. Cell Immunol 40:285-293, Oct 1978

20. Gisler RH, Lindahl P, Gresser I: Effects of interferon on antibody synthesis in vitro. J Immunol 113:438-444, Aug 1974

21. De Maeyer E, De Maeyer-Guignard J, Vandeputte H: Inhibition by interferon of delayed-type hypersensitivity in the mouse. Proc Natl Acad Sci USA 72:1753-1757, May 1975

22. De Maeyer-Guignard J, Cachard A, De Maeyer E: Delayed-type hypersensitivity to sheep red blood cells—Inhibition of sensitization by interferon. Science 190:574-576, Nov 1975

23. Lindahl P, Leary P, Gresser I: Enhancement by interferon of the specific cytotoxicity of sensitized lymphocytes. Proc Natl Acad Sci USA 69:721-725, Mar 1972

24. Imanishi J: Inhibition of macrophage migration by virus-induced interferon preparations. Jpn J Microbiol 19:337-342, Oct 1975

25. Welsh RM Jr: Cytotoxic cells induced during lymphocytic choriomeningitis virus infection of mice—I. Characterization of natural killer cell induction. J Exp Med 148:163-181, Jul 1978

26. Hirsch MS, Ellis DA, Black PH, et al: Immunosuppressive effects of an interferon preparation in vivo. Transplantation 17: 234-236, Feb 1974

27. Gresser I, Maury C, Tovey M: Interferon and murine leukemia—VII. Therapeutic effect of interferon preparation after diagnosis of lymphoma in AKR mice. Int J Cancer 17:647-651, May 15, 1976

28. Frayssinet C, Gresser I, Tovey M, et al: Inhibitory effect of potent interferon preparations on the regeneration of mouse liver after partial hepatectomy (Letter). Nature 245:146-147, Sep 1973

29. Gresser I, Tovey M, Maury C, et al: Lethality of interferon preparations for newborn mice. Nature 258:76-78, Nov 6, 1975

30. Gresser I, Maury C, Tovey M, et al: Progressive glomerulonephritis in mice treated with interferon preparations at birth. Nature 263:420-422, Sep 30, 1976

31. Merigan TC, Sikora K, Breeden JH, et al: Preliminary observations on the effect of human leukocyte interferon in non-Hodgkin's lymphoma. N Engl J Med 299:1449-1453, Dec 28, 1978

32. Gutterman JB, Blumenochen GR, Alexanian R, et al: Leukocyte interferon-induced tumor regression in human metastatic breast cancer, multiple myeloma, and malignant lymphoma. Ann Intern Med 93:399-406, Sep 1980

33. Pauker K, Cantell K, Henle W: Quantitative studies on viral interferons in suspended L cells. Virology 7:324-334, Jun 1962

34. Balkwill FR, Oliver RT: Growth inhibitory effects of interferon on normal and malignant human haemopoietic cells. Int J Cancer 20:500-505, Oct 15, 1977

35. Strander H, Einhorn S: Effect of human leukocyte interferon on the growth of human osteosarcoma cells in tissue culture. Int J Cancer 19:468-473, Apr 1977

36. Lundgren E, Larsson I, Miörner H, et al: Effects of leukocyte and fibroblast interferon on events in the fibroblast cell cycle. J Gen Virol 42:589-595, Mar 1979

37. Creasey AA, Bartholomew JC, Merigan TC: Role of G_0-G_1 arrest in the inhibition of tumor cell growth by interferon. Proc Natl Acad Sci USA 77:1471-1475, Mar 1980

38. Gresser I: On the varied biologic effects of interferon. Cell Immunol 34:406-415, Dec 1977

39. Rossi GB, Dolei A, Capobianchi MR, et al: Interactions of interferon with *in vitro* model systems involved in hematopoietic cell differentiation. Conference on Regulatory Functions of Interferon. Ann NY Acad Sci 350:279-293, 1980

40. Lindahl P, Leary P, Gresser I: Enhancement by interferon of the expression of surface antigens on murine leukemia L1210 cells. Proc Natl Acad Sci USA 70:2785-2788, Oct 1973

41. Killander D, Lindahl P, Lunden L, et al: Relationship between the enhanced expression of histocompatibility antigens on interferon-treated L1210 cells and their position in the cell cycle. Eur J Immunol 6:56-59, Jan 1976

42. Lindahl P, Leary P, Gresser I: Enhancement of the expression of histocompatibility antigens of mouse lymphoid cells by interferon *in vitro*. Eur J Immunol 4:779-784, Dec 1974

43. Lindahl P, Gresser I, Leary P, et al: Interferon treatment of mice—Enhanced expression of histocompatibility antigens on lymphoid cells. Proc Natl Acad Sci USA 73:1284-1287, Apr 1976

44. Gresser I: Metamorphosis of human amnion cells induced by preparation of interferon. Proc Natl Acad Sci USA 47:1817-1822, Nov 1961

45. Knight E Jr, Korant BD: A cell surface alteration in mouse L cells induced by interferon. Biochem Biophys Res Commun 74:707-713, Jan 1977

46. Huet C, Gresser I, Bandu MT, et al: Increasing binding of concanavalin A to interferon-treated murine leukemia L 1210 cells. Proc Soc Exp Biol Med 147:52-57, Oct 1974

47. Brouty-Boye D, Tovey M: Inhibition by interferon of thymidine uptake in chemostat cultures of L 1210 cells. Intervirology 9:243-252, 1978

48. Sonnenfeld G, Meruelo D, McDevitt HO, et al: Effect of type I and type II interferons on murine thymocyte surface antigen expression, induction or selection. Cell Immunol 57:427-439, Jan 1981

49. Nebert DW, Friedman RM: Stimulation of aryl hydrocarbon hydroxylase induction in cell cultures by interferon. J Virol 11: 193-197, Feb 1973

50. Moehring TJ, Moehring JM, Stinebring WR: Response of interferon-treated cells to diphtheria toxin. Infect Immun 4:747-752, Dec 1971

51. Ida S, Hooks JJ, Siraganian RP, et al: Enhancement of IgE-mediated histamine release from human basophils by viruses—Role of interferon. J Exp Med 145:892-906, Apr 1977

52. De Maeyer-Guignard J, De Maeyer E: Electrophoretically pure mouse interferon exerts multiple biologic effects. Conference on Regulatory Functions of Interferon. Ann NY Acad Sci 350: 347-353, 1980

53. Revel M, Kimchi A, Shulman L, et al: Role of interferon-induced enzymes in the antiviral and antimitogenic effects of interferon. Conference on Regulatory Functions of Interferon. Ann NY Acad Sci 350:459-472, 1980

54. Besancon F, Ankel H, Basu S: Specificity and reversibility of interferon gangliosides interaction. Nature 259:576-578, Feb 1976

55. Pitha PM, Vengris VE, Reynolds FH Jr: The role of cell membrane in the antiviral effect of interferon. J Supramol Struct 4:467-473, 1976

56. Revel M, Bash D, Ruddle FH: Antibodies to a cell-surface component coded by human chromosome 21 inhibit action of interferon. Nature 260:139-141, Mar 11, 1976

57. Revel M, Schmidt A, Shulman L, et al: The regulation of protein synthesis by interferon, *In* Rosenthal S (Ed): Gene Functions, 12th FEBS Meeting, Vol 51. Oxford, Pergamon Press, 1979, pp 415-426

58. Farrell PJ, Sen GC, Dubois MF, et al: Interferon action—two distinct pathways for inhibition of protein synthesis by double-stranded RNA. Proc Natl Acad Sci USA 75:5893-5897, Dec 1978

59. Nilsen T, Baglioni C: Mechanism for discrimination between viral and host RNA in interferon-treated cells. Proc Natl Acad Sci USA 76:2600-2604, Jun 1979

60. Cantell K, Hervonen S, Mogensen KE, et al: Human leukocyte interferon—Production, purification and animal experiments—The production and use of interferon for the treatment and prevention of human virus infections, *In* Waymouth C (Ed): *In Vitro*. Baltimore, Tissue Culture Association, 1975, pp 35-38

61. Merigan TC, Gallagher JG, Pollard RB, et al: Short course human leukocyte interferon in the treatment of herpes zoster in patients with cancer. Antimicrob Agents Chemother 19:193-195, 1981

62. Arvin AM, Feldman S, Merigan TC: Human leukocyte interferon in the treatment of varicella in children with cancer—A preliminary controlled trial. Antimicrob Agents Chemother 13: 605-607, Apr 1978

63. Arvin A, Yeager A, Merigan TC: The effect of leukocyte interferon on urinary excretion of cytomegalovirus in infants. J Infect Dis 133(Suppl):A205-210, 1976

64. Scullard GH, Pollard RB, Smith JL, et al: Antiviral treatment of chronic hepatitis B virus infection—I. Changes in viral markers with interferon combined with adenine arabinoside. J Infect Dis 43:772-783, 1981

65. Scullard GH, Andres LL, Greenberg HB, et al: Antiviral treatment of chronic hepatitis B virus infection—III. Improvement in liver disease with interferon and adenine arabinoside. Hepatology 1:228-232, 1981

66. Scullard GH, Greenberg HB, Smith JL, et al: Antiviral treatment of chronic hepatitis B virus infection—II. Infectious virus cannot be detected in patient serum after permanent responses to treatment. Hepatology 1982 (In Press)

67 Sacks SL, Scullard GH, Pollard RB, et al: Antiviral treatment of chronic hepatitis B virus infection. IV. Pharmacokinetics and side effects of interferon and adenine arabinoside alone and in combination. Antimicrob Agents Chemother 1982 (In Press)

68. Louie AC, Gallagher JG, Sikora K, et al: Follow-up observations on the effect of human leukocyte interferon in non-Hodgkin's lymphoma. Blood 58:712-718, 1981

Important Advances in Clinical Medicine

Epitomes of Progress — Neurosurgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurosurgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in neurosurgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurosurgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Early Warnings of Intracranial Aneurysms That Bleed

THE MORBIDITY AND MORTALITY from rupture of intracranial aneurysms are of such magnitude that physicians should be alerted to any identifying clues of impending bleeding. Aneurysms in specific loci may have well-described clinical signs before they bleed. Less precise, but of equal import, are other danger signals of imminent bleeding (or, at least, ominous activity) by the aneurysm that should lead to prompt investigation and preventive treatment.

Prominent among these are so-called minor episodes a few days or weeks before a major bleeding event. Called "warning leaks," their true hemorrhagic nature is not necessarily established, but the symptoms demand attention: usually a severe occipital or nuchal pain (occasionally frontal or retro-orbital) with radiation to the vertex or the spine without loss of consciousness but occasionally with vomiting. Recovery is commonly rapid over about 48 hours.

Sixty percent of patients admitted to King and Saba's series with a subarachnoid bleeding episode reported such telltale clues, and 50 percent of Gillingham and Maccabe's patients admitted in stupor or coma were found to have had warning headaches. Fisher also encountered a history of one or more sudden minor headaches occurring in the four weeks before a major attack in about 25 percent of patients with ruptured saccular aneurysms. Of one to several days' duration, some headaches were associated with stiff neck. Clearly, we must consider such warning episodes of unmistakable diagnostic value. Three recent examples in our clinic, two of which were probably avoidable tragedies, underscore the importance of such symptoms.

Although other signs may herald trouble (such as transient ischemic episodes due to emboli from an aneurysm), complaints of cranial pain—severe headache, often worse than anything the patient had previously experienced—should attract the physician's attention.

The pathogenic mechanisms of such sentinel complaints may not be readily proved, but there is indirect evidence that limited leakage of the aneurysm, bleeding into the wall of the aneurysm without extravasation beyond its confines, weakening and tearing or stretching of the wall of the aneurysmal sac may, individually or collectively, be responsible. Not only is spilled blood irritating to pain-sensitive meninges, but the neural innervation of the dura mater and the great vessels from

which aneurysms arise can be stretched and distorted. These mechanisms undergird the painful symptoms of early warnings.

Failure to recognize the significance of such warning clues may jeopardize the patient's prospects for early preventive treatment.

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REFERENCES

Fisher CM: Clinical syndromes in cerebral thrombosis, hypertensive hemorrhage, and ruptured saccular aneurysm. Clin Neurosurg 1975; 22:117-147

Gillingham FJ: The management of ruptured intracranial aneurysms. Scot Med J 1967 Oct; 12:377-383

King RB, Saba MI: Forewarnings of major subarachnoid hemorrhage due to congenital berry aneurysm. NY State J Med 1974 Apr; 74:638-639

Neonatal Periventricular-Intraventricular Hemorrhage

NEONATAL periventricular-intraventricular hemorrhage (PV-IVH) occurs within the first 24 to 48 hours after birth in 40 percent to 45 percent of premature infants of gestational age less than 32 weeks and birth weight less than 1,500 grams. The hemorrhage originates in the subependymal germinal matrix near the head of the caudate nucleus due to a number of factors. A disproportionate amount of the cerebral blood flow is directed into an immature capillary bed that lacks autoregulation and is subject to fluctuations in systemic arterial blood pressure and intracranial venous pressure. The gelatinous structure of the subependymal matrix predisposes the area to extension of hemorrhage into the adjacent ventricle and into the cerebral parenchyma. Asphyxia, so common to premature infants, appears to aggravate the tendency toward PV-IVH.

The fulminating clinical deterioration that heralds an acute hemorrhagic episode was well recognized in the past, consisting of sudden apnea, bradycardia, seizures, a bulging fontanelle and extensor posturing, accompanied soon thereafter by hypoxemia, hypotension and acidosis. However, the advent of routine cranial computed tomography (CT) scanning and, more recently, ultrasound screening of premature infants has shown that nearly 50 percent of all episodes of PV-IVH have either a saltatory course or a silent clinical picture. As expected, the subtler clinical pictures are associated both with lesser degrees of hemorrhage and better prognoses.

The short-term and long-term prognoses of infants with PV-IVH are directly related to the severity of the hemorrhage as shown by ultrasound or CT scan. Severe hemorrhages, which usually have a parenchymal hematoma and blood filling the ventricles, result in a 50 percent to 65 percent death rate, progressive hydrocephalus in nearly all the survivors and severe neurologic deficits. Therapy has a limited effect on the outcome. However, mild to moderate hemorrhages, which usually involve a variable amount of intraventricular hematoma, are associated with survival in most of these patients. They still have, however, a 10 percent to 25 percent chance of progressive hydrocephalus. Therapy is directed toward the maintenance of normal oxygenation and acid-base balance and of normal cerebral perfusion pressure by avoiding systemic hypotension or hypertension and by relieving intracranial pressure by ventricular taps or lumbar punctures. Shunting procedures may be required in a small percentage of survivors in whom progressive ventricular dilatation develop despite repeated lumbar-puncture drainage.

Ultimately the best management of neonatal PV-IVH is to prevent its occurrence by developing techniques to avoid premature birth. Until then, rapid diagnosis of a hemorrhagic event by ultrasound or CT scan, treatment that maintains normal cerebral metabolism and perfusion, and detection and treatment of posthemorrhagic hydrocephalus gives the best prognosis for normal development in these unfortunate patients.

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REFERENCES

Ahmann PA, Lazzara A, Dykes FD, et al: Intraventricular hemorrhage in the high-risk preterm infant: Incidence and outcome. Ann Neurol 1980 Feb; 7:118-124

Papile LA, Burstein J, Burstein R, et al: Incidence and evolution of subependymal intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. J Pediatr 1978 Apr; 92:529-534

Volpe JJ: Neonatal intraventricular hemorrhage. N Engl J Med 1981 Apr 9; 304:886-891

Wigglesworth JS, Pape KE: Pathophysiology of intracranial hemorrhage in the newborn. J Perinat Med 1980; 8:119-133

Adult Dementia—Treatable Hydrocephalus?

PROGRESSIVE DEMENTIA accompanying communicating hydrocephalus, at times with a normal or near-normal pressure of the cerebrospinal fluid (CSF), has been identified as a condition that is potentially treatable by a variety of CSF shunting procedures (for example, ventriculoperitoneal shunt) that permit CSF drainage. With this condition there is a gradual progression, typically over weeks or months, of impairment of intellect and memory, along with psychomotor retardation, advancing to a severe dementia, often accompanied by an ataxic or apraxic gait disturbance and urin-

ary incontinence. Patients may not have headache and may have no apparent signs of increased intracranial pressure. There may be preceding events such as subarachnoid hemorrhage, trauma or meningitis. In some cases the condition may develop coincident with the growth of a neoplasm; in other instances there is no recognizable cause.

Data derived from pneumoencephalographic and isotope cisternographic studies may suggest that normal-pressure hydrocephalus represents a type of communicating hydrocephalus with an insufficiency of the subarachnoid spaces over the convexities, resulting in an impairment in the circulation and absorption of spinal fluid. Computed axial tomography may show large ventricles often accompanied by obliteration of the subarachnoid cisterns and absence of evidence of cortical atrophy. Isotope cisternography frequently elucidates the CSF pathways in hydrocephalus. The isotope after injection into the lumbar sac will reflux into the ventricular system in patients with communicating hydrocephalus, while in normal people it will continue above the hemispheric convexities. False-negative and false-positive results are common, however, and the presence of ventricular reflux has not been clearly shown to determine which patients are likely to improve after a shunt. Water-soluble contrast agents such as metrizamide used in conjunction with computed tomography may provide a reliable image of the CSF pathways in patients with hydrocephalus.

Surgical therapy has been the most efficacious treatment, with ventriculoperitoneal shunt being so far the most widely used of many different procedures that have been advocated for the amelioration of hydrocephalus.

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REFERENCES

Adams RD, Fisher CM, Hakim S, et al: Symptomatic occult hydrocephalus with "normal" cerebrospinal fluid pressure—A treatable syndrome. N Engl J Med 1965 15 Jul; 273:117-126

Fishman RJ: Cerebrospinal Fluid in Diseases of the Nervous System. Philadelphia, WB Saunders, 1980, pp 95-107

Stein SC, Langfitt TW: Normal-pressure hydrocephalus—Predicting the results of cerebrospinal fluid shunting. J Neurosurg 1974 Oct; 41:463-470

CSF Leak After Head Injury

CEREBROSPINAL FLUID (CSF) leak, and the attendant risk of central nervous system infection, is a potentially devastating complication of simple basilar skull fractures. CSF leak can be difficult to recognize soon after injury. Because CSF draining from the nose or ears is admixed with blood, which contaminates the results of dip-stick glucose testing or chemical analysis, laboratory tests are usually indeterminate. Although the halo sign (a drop of fluid on filter paper forming a clear or pink ring of CSF around a discrete, red circle of blood) may provide early evidence, CSF leakage becomes more obvious 12 to 18 hours after injury, after overt bleeding ceases.

Conservative measures can slow or stop CSF loss. Elevating the head and avoiding Valsalva maneuvers, bending or lifting diminish CSF hydrostatic forces. Fluid restriction (20 ml per kg of body weight a day for adults) and acetazolamide (250 mg daily) diminish CSF production. We administer 16 million units of penicillin daily in adults (ampicillin in children) while leakage is active, though this treatment has not been proved efficacious and is not used in all institutions.

If leakage persists longer than four days, we drain CSF for three to five days, using a fine lumbar subarachnoid catheter introduced percutaneously via a Tuoy needle found in spinal epidural anesthesia sets. This temporary CSF diversion usually stops the leak, but it often causes severe headache and requires caution. If leakage continues longer than 14 days, the exact site of leakage must be found and surgical repair considered. X-ray studies are of minimal value. Thin-section computerized tomography (CT) or complex polytomography may define the fistula. Isotope cisternography sometimes locates a lesion to a general area, but metrizamide isotope cisternography with a high-resolution CT scanner will show the exact site of leakage in most cases.

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REFERENCE

Naidich TP, Moran CJ: Precise anatomic localization of atraumatic sphenoethmoidal cerebrospinal fluid rhinorrhea by metrizamide CT cisternography. J Neurosurg 1980 Aug; 53:222-228

New Surgical Approaches to the Numb Face

COMMON CAUSES of facial numbness include exposure to cold, hyperventilation, hysteria, tumor, stroke, demyelination and trauma. Some are reversible, but others are not and treatment may vary from no treatment to complicated intracranial surgical procedures. Accurate diagnosis can usually be made by examination in the office.

Bilateral numbness of the face without other sensory or motor deficits is commonly caused by hyperventilation or hysteria. While unilateral numbness may be caused by hysteria, it may also be associated with a specific lesion of the trigeminal nerve, ganglion or brain-stem nuclei. If numbness corresponds anatomically to one or more of the

three trigeminal divisions, it is likely caused by a lesion of the nerve itself or one of its branches. Progressive numbness suggests a neoplasm, while an intermittent, fluctuating course implies multiple sclerosis. A fixed, stable deficit, particularly when sudden in onset and associated with other neurologic deficits, suggests focal ischemia, most likely at the brain-stem level.

New surgical approaches to lesions causing facial numbness employ an operating microscope. Many tumors, including neurinomas and meningiomas, can now be removed safely and completely because the anatomy is better seen and surgical technique is more refined. Revascularization procedures, such as microanastomosis of the occipital artery to a branch of the vertebrobasilar system, are being used to treat focal ischemia of the brain stem. Traumatized nerves, including branches of the trigeminal, can be repaired with great accuracy with currently available methods. And, current research in multiple sclerosis holds great promise for effective treatment of that disorder in the not-too-distant future.

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REFERENCES

Ausman JI, Lee MC, Chater N, et al: Superficial temporal artery to superior cerebellar artery anastomosis for distal basilar artery stenosis. Surg Neurol 1979 Oct; 12:277-282

Poser CM, Alter M, Currier RD, et al: Common demyelinating and degenerative diseases and extrapyramidal disorders—Panel 4. Arch Neurol 1979 Nov; 36:759-770

Paresthesias in the Hands

PARESTHESIAS IN THE HANDS, even without cyanosis or blanching of the fingers, can be disabling. Neurologic evaluation is required, and in some cases the symptoms are most effectively treated by neurosurgical methods. While paresthesias in the hands can be caused by an abnormality located anywhere between the postcentral cerebral cortex and the peripheral nerves in the hands, the most common causes are a few well-known entities located in the cervical spine or upper extremities.

Paresthesias following neck trauma require careful neurologic and radiologic evaluation for possible fracture, dislocation or subluxation. Cineradiography or tomographic studies may be required. In patients with rheumatoid arthritis, atlantoaxial subluxation is a possibility.

Cervical disc disease is probably the most common cause of the paresthesias. The paresthesias may be less in severity than pain in the neck, shoulder and arm. Weakness in arm or forearm muscles is often present. Once the diagnosis is certain, most cases can be satisfactorily treated by nonsurgical methods, that is, some degree of rest and immobilization. Those cases that fail to improve with conservative therapy usually require myelographic studies. It is possible that computerized tomographic (CT) scanning will gradually replace myelography for this type of diagnostic study.

When the brachial plexuses are the source of hand paresthesias, the symptoms are less severe than with cervical disc disease. Both thoracic outlet syndrome and scalenus anticus syndrome are well-described entities that rarely require surgical treatment except in those cases in which cervical ribs are present and give rise to progressive motor or sensory impairment or arterial insufficiency. Tumors, both primary and metastatic, can involve the brachial plexuses, but pain is then more severe.

Next to cervical disc disease, the most common cause of hand paresthesias is carpal tunnel syndrome. Paresthesias characteristically awaken the patient at night and are in the median nerve distribution. Thenar atrophy and weakness of grasp may be noted. This condition can be associated with other diseases, such as diabetes, hypothyroidism, rheumatoid arthritis and acromegaly. Some activities predispose to carpal tunnel syndrome, for example, pruning, knitting, painting and piano playing. Electromyography (EMG) and nerve conduction studies can be very helpful in elucidating the diagnosis. Splinting the wrist usually alleviates nocturnal paresthesias. Operation for carpal tunnel syndrome is usually advised if there is thenar weakness or atrophy and if satisfactory relief of paresthesias is not maintained after a trial of splinting. Injection of steroids into the wrist or given orally usually provide only temporary relief.

Compression of the ulnar nerve, either at the elbow or at the wrist, from a variety of entrapment syndromes can produce paresthesias in the ulnar distribution and weakness in the ulnar-innervated muscles. These conditions require careful neurologic study, including EMG and nerve conduction studies, to identify the location of the abnormality along the course of the nerve. Frequently it is found in the olecranon, medial epicondyle and antecubital portions of the nerve distribution. The neuropathy may be relieved by surgical removal of entrapping bands or by moving the nerve to a shorter, more anterior course.

Peripheral neuropathies such as in diabetes, hypothyroidism and toxic neuropathies (alcohol, organic solvents or vincristine sulfate) can produce hand symptoms but usually only after paresthesias

are present in the feet. Other neurologic conditions such as multiple sclerosis can cause paresthesias in the absence of other signs or symptoms.

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REFERENCES

Crawford FA Jr: Thoracic outlet syndrome. Surg Clin North Am 1980 Aug; 60:947-956

Gelberman RH, Aronson D, Weisman MH: Carpal tunnel syndrome—Results of a prospective trial of steroid injection and splinting. J Bone Joint Surg 1980 Oct; 62:1181-1184

Mayfield FH: Cervical spondylotic radiculopathy and myelopathy. Adv Neurol 1979; 22:307-321

Symptoms Suggesting Brain Tumors

THE AVAILABILITY of computed tomographic (CT) scanning has revolutionized the diagnosis and treatment of brain tumors and has increased awareness of the diversity of clinical symptoms. In the past, detailed autopsy series have revealed approximately ten brain tumors per 100,000 people while clinical reports have suggested approximately half this incidence. Appreciation of the unusual clinical presentations of some of these tumors may insure that a higher proportion will be identified during life.

Symptoms of brain tumors can be divided into four general categories: headache and nausea, seizures, focal neurologic deficit and mental changes. Although headaches occur in most tumors, evaluation in patients with only headaches rarely identifies one. This is particularly true when funduscopic examination reveals venous pulsations and no papilledema.

Seizures are very common in patients with slowly growing tumors of the brain parenchyma and occur in many cases of extraparenchymal tumors and in about a third of rapidly growing tumors. CT scanning has identified tumors in approximately 10 percent of patients examined for adult-onset seizures.

Focal neurologic deficits are abnormalities of function which identify a lesion in a specific area of the brain. Examples of focal neurologic deficits are unilateral weakness or unilateral hearing loss. These types of deficits occur in most brain tumors. However, small tumors, those in "silent" areas of the brain and tumors outside the brain but within the skull may not produce focal deficits.

Mental changes are common in very large and in rapidly growing tumors, particularly if located in the frontal lobes.

Traditional teaching is that tumors are characterized by a slow but steady progression of neurologic symptoms. This is not always the case. A third of patients with brain tumors are initially thought to have strokes; tumors cause 5 percent to 10 percent of spontaneous intracerebral hemorrhages.

We recommend investigation of patients by contrast-enhanced computed tomography if one or more of the following are present: headache with loss of retinal vein pulsations, papilledema, adult-onset seizures, focal neurologic deficit (unless a peripheral nerve or spinal cause is apparent) or progressive mental changes. This procedure should identify nearly all intracranial tumors.

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REFERENCES

Cobb CA, Youmans JR: Glial and neuronal tumors of the brain in adults, *In* Youmans JR (Ed): Neurological Surgery, 2nd Ed. Philadelphia, WB Saunders, 1981, pp 2759-2835

Gall MV, Becker H, Hacker H: Die Computer-Tomographie in der Diagnostik der Epilepsie. Nervenarzt 1977; 48:72-76

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EDITORIALS

The Risks and Benefits of Heparin Therapy

IT IS ASTONISHING and somewhat chastening to realize that more than 40 years after its introduction into clinical medicine, heparin remains a source of continuing controversy. Although the areas of disagreement have narrowed, there is still no widely accepted consensus on the optimal mode of administration, the proper dose, the most appropriate mode of monitoring, the clinical indications for and the risks of heparin. The reasons for persisting uncertainty are not particularly obscure. Studies of the best route of administration have yielded different conclusions. No single trial has established a correlation between dose and efficacy. No method of monitoring heparin has emerged as clearly the most useful. Most important, while virtually all clinicians would agree that heparin reduces the frequency of initial and recurring pulmonary emboli, their abiding perception of the hazards of heparin therapy makes them both reluctant to use heparin and willing to ascribe to it complications that might well have occurred even in its absence.

In this setting the report by Nelson and his associates, appearing in this issue, is particularly helpful, for it describes the actual outcome of a year's experience with full-dose heparin therapy in a major academic teaching hospital. The fact that the experience was uncontrolled (and, therefore, not subject to the well-known Hawthorne effect, in which the very act of conducting a trial improves the outcome), makes the report at least as valuable as yet another potentially inconclusive, prospective, controlled study.

Somewhat to the authors' surprise, their staff had adopted only one mode of administration—continuous intravenous infusion—and only one method of monitoring the dose—the activated partial thromboplastin time. Although their report provides many provocative glimpses at the discrepancies between a theoretically optimal plan for heparin administration and actual practice even on a first-class teaching service, we should note in particular two other observations that may also be extended to most hospital settings.

First, the major and minor risks of heparin therapy are predominantly concentrated in that set of patients who have significant intercurrent disease and who are over 60. The obverse needs to be stated as well. The risks of major complications of heparin therapy are minimal (but certainly not absent) in those patients under the age of 60 who have no illness other than the one (usually deep venous thrombosis or pulmonary embolism, or both) for which heparin is given. Their second finding also warrants explicit emphasis: in those patients treated for deep venous thrombosis and pulmonary embolism, clinically detectable thromboembolism did not recur.

Taken together, these two observations show once again that in those patients whose primary diagnosis is established or suspected deep venous thrombosis or pulmonary embolism, heparin is a highly effective and acceptably safe mode of therapy. Conversely, in those elderly patients with serious illness in addition to suspected or established venous thromboembolic disease, heparin

may be a less effective and a high-risk type of therapy. The observations also suggest that the outcome of a specific mode of heparin therapy may be determined as much by the characteristics of the patient population being studied as by the specific intervention.

Perhaps it is appropriate to acknowledge that in prior studies excessive emphasis may have been placed on the technical aspects of heparin therapy and less than necessary attention given to basic precepts of clinical judgment. In the appropriate patients, undue concern for the risks of heparin should not delay heparin administration. Nelson's data illustrate the relative safety of giving a short course of heparin until the appropriate data base is obtained. When a patient with advanced metastatic disease experiences a major pulmonary embolism, however, the appropriate therapeutic decision should encompass compassion and clear-headed analysis of the risks of therapy, as well as the dictates of controlled clinical trials.

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Do We Need to 'Open Up' the Health Care System?

IN A COMMENTARY appearing elsewhere in this issue, Dr. Arthur Rivin discusses a controversial report commissioned by California's Board of Medical Quality Assurance (BMQA) and then subsequently rejected by it, and notes that there still remain those who believe that the present California Medical Practice Act "needs substantial revision to reflect a more appropriate balance between the protection of the public and unnecessary limitation of individual freedom." The issues being raised are not to be overlooked and in today's political, economic and social environment it is probable that they will remain with us for some time. And, if comparable issues in the past are any precedent, it is unlikely that they will remain confined just to California.

Laws that govern medical practice are enacted for the protection of the public and, since they allow physicians who are licensed to do things that others are not permitted to do, they also protect physicians. However, in recent years medicine and health care have more and more become viewed as "everybody's business." Rising costs undoubtedly have had something to do with this, but probably even more important has been the wide and open dissemination of medical information, both proved and conjectural, to patients and to the public. The responsibility for the what, why and how of health care has necessarily come to be shared by more and more kinds of health professionals (who now are often seeking to expand their scope of practice) and more and more of the public who are now often seeking out unconventional and unproved (and frequently costly) health regimens in their quest for cures or just to feel better. Thus among health professionals and among the public there are now those who believe the law is unjustifiably protective of physicians and is depriving the public of some services nonmedical practitioners are prepared, or believe they are prepared, to render.

The medical profession is finding itself on the defensive, seeking to preserve its turf and role in health care, which it genuinely believes to be in the best interests of patient care and better health for the public. In his commentary Dr. Rivin touches upon one of the reasons this is so. Good patient care and good health care for the public depend on good diagnosis and well-carried out treatment appropriate to the diagnosis. This requires the broad medical knowledge, the practice skills and the accumulated experience that is characteristic of physicians. And today's health care consumer or even today's allied health professional is seldom as well-informed or as well-qualified to perform these functions as are today's physicians. It is therefore clearly in the public's interest to protect the turf and role of licensed physicians and surgeons in health care. By definition, there can really be no adequate substitute.

—MSMW

Menopause—A Medical Challenge

USING SURVIVAL PROBABILITY for 17th century European populations, it can be estimated that 28 percent of the women lived to experience menopause but only 5 percent survived to age 75. In the 20th century, however, 95 percent of women in developed countries may expect to reach meno-

pause and 50 percent to reach the age of 75. Thus, fully a third of a woman's life may be spent in the absence of ovarian estrogen production and with its associated biological consequences. The fact that more than 30 million women in the United States alone are of menopausal age emphasizes the importance of understanding functional menopausal changes.

Despite the global nature of this problem, remarkably little is known about the physiology of menopause. An adequate understanding is impeded by the lack of basic information concerning the general aging process, to which menopause is intimately related.[1] Moreover, both menopause and aging are influenced by social, environmental and emotional factors that are difficult to treat analytically. However, recent observations, both clinical and mechanistic, have added a new dimension to dealing with biomedical problems of menopause.

The article "The Menopause" by Brenner in this issue is reflective of our expanding knowledge and comprehension of estrogen replacement in menopausal and postmenopausal women. The flurry about the association of estrogen use and the high incidence of endometrial cancer reported in the mid-1970's has since been reappraised through better controls, critical review of histology reports and belated awareness of the pharmacologic nature of estrogen dosage prescribed. Equally important is the application of progestin in the regimen to counteract the mitogenic action of unopposed estrogen on the endometrium. Much work remains to be done, with the aim being to provide just the right amounts of each for replacement therapy, and with the consideration that endogenous estrogens are produced in varying amounts, particularly in obese postmenopausal women.

Just why estrogen deprivation produces several well-predicted consequences in women is not entirely clear but answers are likely to come about in the near future as intense research is under way. A few important clues have already surfaced that are helpful to patients and physicians in planning the long-term management of the postmenopausal state—a physiologic condition that demands intelligent medical care.

The occurrence of flush episodes is a common component of the menopausal syndrome. Hot flushes can now be measured objectively by monitoring changes in finger temperature via a small thermistor. Recent neuroendocrine studies have given insight into the central mechanism of the transient dysfunction of thermoregulation and have linked the hot flush to pulsatile luteinizing hormone (LH) secretion.[2,3] The duration of a flush averages 2.7 minutes. Flushes are associated with a mean increase in finger temperature of 3.9°C (7.5°F) and with a mean increase in pulse rate of nine beats per minute. All flushes are accompanied by perspiration of a varying degree. In these studies, a near synchrony between flushes and LH pulses was disclosed. The mean interval between LH pulses was found to be 73.5 minutes (range 54.5 to 120 minutes) and the women with the most frequent pulses had the highest frequency of flushes. LH pulses are not always accompanied by flushes. Conversely, however, a flush has not been found to occur in the absence of an LH pulse. LH release by the pituitary per se can be excluded as the cause of flushes because flushes do occur in women who have had hypophysectomies. It seems likely, therefore, that a hypothalamic mechanism must initiate both pulsatile release of LH and flush episodes. Increased finger temperature (vasodilatation) and perspiration observed during flushes suggest transient dysfunction of thermoregulation occurring simultaneously with pulsatile LH release. Since the medial preoptic anterior hypothalamic area and the arcuate nucleus are sites for control of thermoregulation and luteinizing hormone releasing factor (LRF) respectively, the genesis of flush episodes may involve neuroendocrine mechanisms common to both of these two hypothalamic regions.

It is also unlikely that pulsatile LRF itself is responsible for initiation of flushes. Women with gonadal dysgenesis, who have never had normal levels of endogenous estrogen, do not experience flushes even at advanced age. However, when estrogen is administered for several months and then discontinued, these women experience classical menopausal flushes for the first time. This observation suggests that menopausal flushes are a manifestation of a classic withdrawal syndrome, mediated through functional changes of estrogen-sensitive neurons, which are linked to the control of pulsatile LRF and to thermoregulation.

The neuroendocrine mechanism underlying this link is obscure. Active investigations are being carried out on the role of central (but not peripheral) adrenergic mechanisms and the hypothalamic β-endorphin system. These neurotransmitters have similar effects on temperature regulation and

gonadotropin-releasing hormone (GN-RH) secretion. An association between flush episodes and the fluctuation of adrenal steroids has also been observed, suggesting either adrenocorticotropic hormone (ACTH) secretion or an increased blood flow to the adrenal cortex.[4]

Undoubtedly, estrogen replacement abolishes flush episodes. However, an alternate therapy needs to be found because, in a significant number of postmenopausal women, estrogen administration is contraindicated. To this end, it has been shown that synthetic progestins (medroxyprogesterone acetate) appear to be as effective as estrogen.[5]

The long-term and more serious consequence of estrogen deficiency is the accelerated bone loss (resorption) of which the result is osteoporosis.[6] It now has been convincingly shown that the administration of replacement doses of estrogen prevents or at least slows down the osteoporotic process in castrated young and postmenopausal older women.[7] A clear understanding of this beneficial effect of estrogen is not yet at our disposal. However, advances in the understanding of endocrine control of calcium homeostasis have provided a basis for characterization of postmenopausal osteoporosis. In the three target organs, gut, kidney and bone, parathyroid hormone (PTH) acts directly on bone to enhance calcium mobilization, an action opposed by calcitonin. PTH also decreases calcium excretion by the kidney and promotes calcium absorption by the gut. This latter effect is mediated indirectly through PTH-induced production of 1,25-dihydroxycholecalciferol [1,-25-$(OH)_2$D] that in turn acts to enhance calcium absorption from the gut.

There appears to be an age-related reduction of calcium absorption from gut, and a relative deficiency of calcitonin[8] and 1,25-$(OH)_2$D.[9] These findings would suggest that a negative calcium balance develops with advancing age, a change found to be more obvious in women than men and in women with osteoporosis than in normal controls. To maintain normal levels of ionized calcium, depletion of calcium from the bone takes place and results in osteoporosis. It remains to be shown that estrogen deficiency accelerates these hormonal factors in the control of calcium homeostasis. Since estrogen receptors have not been found in the bone cells,[10] the beneficial effect of estrogen may be in part due to an increased calcitonin level that decreases bone resorption.[11] Nonetheless, the preliminary understanding of a relative deficiency of calcium-regulating hormones and the beneficial effect of an increased calcium intake and exercise, together with appropriate estrogen-progestin replacement, may predictably reduce both the number of aged women suffering from osteoporosis and the severity of the condition in the next decade.

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REFERENCES

1. Yen SSC: The biology of menopause. J Reprod Med 1977 Jun; 18:287-296

2. Casper RF, Yen SSC, Wilkes MM: Menopausal flushes: A neuroendocrine link with pulsatile luteinizing hormone secretion. Science 1979 Aug 24; 205:823-825

3. Tataryn IV, Meldrum DR, Lu KH, et al: FSH and skin temperature during the menopausal hot flash. J Clin Endocrinol Metab 1979 Jul; 49:152-154

4. Meldrum DR, Tataryn IV, Frumar AM, et al: Gonadotropins, estrogens and adrenal steroids during the menopausal hot flash. J Clin Endocrinol Metab 1980 Apr; 50:685-689

5. Schiff I, Tulchinsky D, Cramer D, et al: Oral medroxyprogesterone in the treatment of postmenopausal symptoms. JAMA 1980 Sep 26; 244:1443-1445

6. Nordin BEC, Aaron J, Speed R, et al: Bone formation and resorption as the determinants of trabecular bone volume in postmenopausal osteoporosis. Lancet 1981; 1:277-280

7. Christiansen C, Christensen MS, Transbol IB: Bone mass in postmenopausal women after withdrawal of oestrogen/gestagen replacement therapy. Lancet 1981; 1:459-462

8. Deftos LJ, Weisman H, Williams GW, et al: Influence of age and sex on plasma calcitonin in human beings. N Engl J Med 1980 Jun 12; 302:1351-1353

9. Slovik DM, Adams JS, Neer RM, et al: Deficient production of 1,25-dihydroxyvitamin D in elderly osteoporotic patients. N Engl J Med 1981 Aug 13; 305:372-374

10. Chen TL, Feldman D: Distinction between alpha-fetoprotein and intracellular estrogen receptors: Evidence against the presence of estrogen receptors in rat bone. Endocrinology 1978 Jan; 102:236-244

11. Hillyard CJ, Stevenson JC, MacIntyre I: Relative deficiency of plasma-calcitonin in normal women. Lancet 1978 May 6; 1: 961-962

Decision Making in Health Care—Some Ramifications of Interdependence

ONE OF THE major challenges for human society in the remaining years of the 20th Century, and even beyond, will be to find ways to deal effectively with the reality of social, economic, political and technologic interdependence without unduly compromising individual and local independence and autonomy. The reality of interdependence and its ramifications have yet to be fully recognized, let alone fully understood, and efforts to manage interdependence within a framework of independence (or vice versa) have generally been unsuccessful. So far no one, here or abroad, seems to have found a good way of dealing with this seminal problem.

In this country medicine and the health care

enterprise seem to have been and are to be in the vanguard where issues of independence and interdependence are becoming more evident, and there have been some attempts to deal with them. Someone has said that the health care enterprise in this nation is a system, not a nonsystem, because if you push it (or repress it) in one place it always bulges out somewhere else. In any case it is noteworthy that in health care unrestricted free enterprise did not work well (too many people did not receive any or sufficient care). Federal financing and federal regulation have not worked well (tending to be too costly, too inefficient and too inflexible). And now we are about to try something in between called "procompetition," which may or may not work either. The permutations and combinations of blending free enterprise (independence) with government regulation and hierarchical control (of interdependence) are virtually limitless, and this may well go on and on.

It would seem that experience to date suggests that no one element in an interdependent system (social, economic, political, technologic) can independently impose its will upon all the other independent and generally autonomous elements of such an interdependent system and make it work. And for health care this includes the medical profession at one extreme and the federal government at the other. Neither has been able to achieve authoritative control of health care. A corollary of this would seem to be that in a relatively interdependent system made up of relatively independent entities, such as is the case with the health care enterprise, the independent entities (the ones that will do whatever is to be done) must somehow be involved in first agreeing that there is a problem, and then deciding what can and should be done about it, and finally reaching agreement on who is to do what to solve it. Interestingly, this is what now occurs in everyday patient care within the framework of informed consent. Patient care today is a free and independent collaborative effort among physician, patient, other health professionals and any appropriate elements of the health care enterprise. Something like informed consent—that is, a free and independent collaborative effort—can and should be true of the health care enterprise itself, including all of its major constituents, of which government is surely one, but only one. In this way the problems of interdependence can be met with a collaborative intervention that is agreed upon by all those autonomous and independent persons or groups that are concerned.

Perhaps the time has come to accept this idea that all who must carry out a health care decision should be involved or represented in the decision process. This means that physicians, along with others, should be involved or represented in consensus or decision making at every level and in every aspect of patient care and health care. If such a process could be tried and made to work for health care and the health care enterprise, it could then become a model for the exercise of freedom and independence within the broader interdependent social, economic, political, technologic system, and perhaps thus an answer to one of the major challenges facing today's free society.

The Council for Medical Affairs, sponsored as it is by the Association of American Medical Colleges (AAMC), the American Medical Association (AMA), the American Hospital Association (AHA), the American Board of Medical Specialties (ABMS) and the Council of Medical Specialty Societies (CMSS) might be an appropriate agency to take the lead and to show the way.

—MSMW

CASE REPORTS

Refer to: Gesundheit N, Kent DL, Fawcett HD, et al: Infected liver cyst in a patient with polycystic kidney disease. West J Med 136:246-249, Mar 1982

ABBREVIATION USED IN TEXT

PKD = polycystic kidney disease

Infected Liver Cyst in a Patient With Polycystic Kidney Disease

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LIVER CYSTS are present in approximately 30 percent of patients with autosomal dominant polycystic kidney disease (PKD).[1,2] These cysts are usually asymptomatic and do not impair liver function.[2] Rare complications of liver cysts in patients with PKD include portal hypertension with bleeding esophageal varices[3,4] and hepatic failure with encephalopathy.[5]

Infection of liver cysts in patients with PKD is extremely rare. Abscess formation in multiple liver cysts has been reported as a postmortem finding in two patients with PKD who died from complications of abdominal surgical procedures.[6,7] We report the case of a patient with autosomal polycystic kidney disease who had fever and abdominal pain and was found to have an infected liver cyst. The patient was treated successfully with surgical drainage of the cyst and administration of antibiotics.

Report of a Case

A 59-year-old man with autosomal dominant polycystic kidney disease was admitted to the Veterans Administration Medical Center, Palo Alto, California, in May 1980 because of fatigue, malaise and daily fever. The patient's polycystic kidney disease was diagnosed in 1956 by intravenous pyelography after several episodes of urinary tract infection. Between 1956 and 1974 he was in good health except for well-controlled hypertension and recurrent episodes of hematuria. In 1975 he began hemodialysis because of declining renal function. He became totally anuric in 1979. Five days before admission to hospital, the patient noted onset of fatigue, malaise and fever. After two days of illness, right upper quadrant pain developed that was sharp, nonradiating and worsened by cough. A culture of blood obtained during hemodialysis grew *Escherichia coli* and the patient was admitted.

On physical examination on admission, the man appeared to be well-developed and anicteric and had complaints of abdominal pain. Blood pressure was 128/72 mm of mercury, pulse 96 beats per minute and temperature 39.6°C (103.2°F). Pertinent physical findings included a patent hemodialysis access shunt in the left femoral area without erythema. The abdomen had active bowel sounds and was soft without guarding or rebound tenderness. There was tenderness to palpation in the right upper quadrant and to percussion in the right lower rib cage. Both kidneys were palpable, multilobular and slightly tender. There was mild costovertebral angle tenderness bilaterally. Rectal examination was within normal limits.

Laboratory results showed a hematocrit of 34 percent and a leukocyte count of 6,900 per cu mm with 65 percent polymorphonuclear leukocytes and 8 percent band forms. Serum electrolytes included a sodium of 136 (135 to 145), potassium 5.1 (3.5 to 5.0), chloride 94 (100 to 106) and bicarbonate 22 mEq per liter (24 to 30). Blood urea nitrogen (BUN) was 99 (normal 10 to 25), serum creatinine 17.9 (1 to 1.5) and serum glucose 101 mg per dl (70 to 110). Alka-

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line phosphatase, serum aspartate aminotransferase (formerly serum glutamic oxaloacetic transaminase, SGOT), serum alanine aminotransferase (formerly serum glutamic pyruvic transaminase, SGPT), lactic dehydrogenase (LDH) and serum bilirubin were within normal limits. Chest x-ray films were normal and electrocardiogram was unchanged compared with one a year before. X-ray films of the abdomen were remarkable for enlarged, multilobular renal contours. No liver shadow was visible.

Therapy was begun with the administration of gentamicin sulfate intravenously. Further studies were conducted over the ensuing days. Ultrasonography of the abdomen showed a normal gallbladder, polycystic kidneys and scattered liver cysts. Computerized tomographic scan of the upper abdomen confirmed the presence of multiple hepatic cysts, the largest of which was seen in the posterolateral portion of the right lobe and measured 6 cm at its greatest diameter (Figure 1, arrows).

After informing the patient of the nature of the procedure and obtaining a signed consent, an indium 111-labeled oxine leukocyte scan was carried out 18 hours after the injection of labeled autologous leukocytes. The method of cell labeling, adapted from Thakur and co-workers,[8] has been described by McDougall and associates.[9] The leukocyte scan (Figure 2, left) showed intense uptake in the upper posterolateral aspect of the right lobe of the liver (arrow). The rest of the liver showed less activity relative to the spleen than is normally seen. A technetium 99m sulfur colloid liver scan (Figure 2, right) done at the same time showed multiple small defects throughout the liver plus a larger defect (arrow) at the same location as on the leukocyte scan.

The patient was given a trial of metronidazole for possible amebic infection, but his fever and malaise persisted. On the ninth hospital day laparotomy and surgical drainage of the infected cyst was carried out. At operation the gallbladder appeared normal and had no palpable stones. Tan foul-smelling pus was aspirated from a cyst on the posterolateral aspect of the right lobe of the liver. On culture, this fluid grew *E coli* with identical antibiotic sensitivities to the organism cultured from the blood. A drain was placed during the operation and gentamicin and clindamycin continued to be administered until the 25th postoperative day. At this point the drain was removed and the antibiotic therapy was discontinued. The patient remained afebrile and was discharged without fever or other symptoms after one week of observation.

Comment

Pyelonephritis is a frequent complication in polycystic kidney disease[10] and infection of renal cysts has been increasingly recognized since the advent of gallium 67 scintigraphy.[11] In addition,

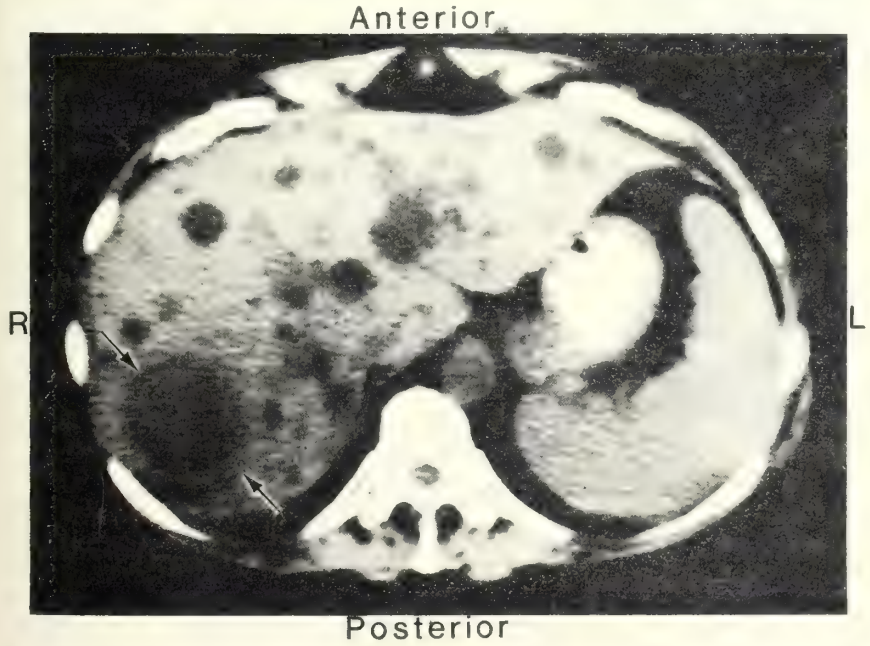

Figure 1.—Computerized tomographic scan of the abdomen at the level of the 11th thoracic vertebra showing multiple hepatic cysts (radiolucent areas). The largest cyst (**arrows**) is located on the posterolateral aspect of the right lobe of the liver and measures 6 cm at its greatest diameter.

perinephric abscess formation following urinary tract infection has been reported in PKD patients on continual hemodialysis.[12]

In contrast, infection of hepatic cysts in patients with PKD is rare. In the two previously reported cases, abdominal surgical procedures not involving the liver were followed by postoperative sepsis and overt liver failure.[6,7] Only at autopsy were multiple cystic abscesses of the liver detected. In the current case, the recent operation did not antedate the cyst infection and early detection led to institution of appropriate therapy.

Recent reports in the literature indicate that indium 111-labeled leukocyte scanning is a clinically useful method for detecting inflammatory diseases and abscesses.[9] Radioactive labeled leukocyte scanning is often particularly useful in locating abdominal abscesses in patients in whom the clinical suspicion is high.[13] In addition, the diagnosis of hepatic abscess and differentiation from hepatic tumor with indium 111-labeled leukocyte imaging has been described.[14] In this patient, the leukocyte scan permitted the detection and diagnosis of an infected cyst in the presence of multiple hepatic cysts.

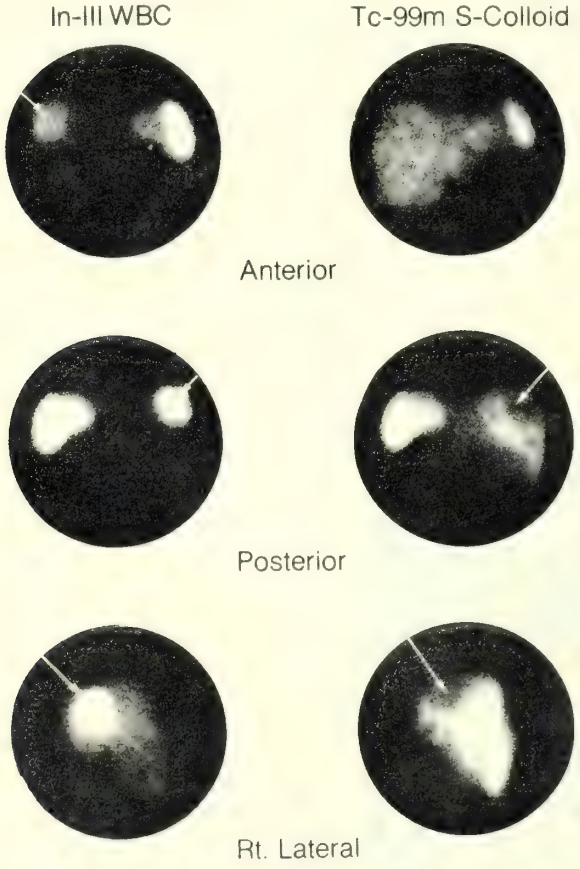

Figure 2.—Indium 111-labeled leukocyte scan (**left**) showing intense uptake in the upper posterolateral portion of the right lobe of the liver at the site of an infected cyst (**arrow**). The technetium Tc 99m sulfur colloid scan (**right**) shows multiple cold lesions throughout the liver due to cysts and a larger defect (**arrow**) corresponding to the infected cyst.

The cause of the isolated infection of a cyst in our patient's polycystic liver is unknown. Anuria precluded urine culture. No skin or pulmonary source of bacteremia was identified. There had been no recent surgical procedure and there was no evidence of cholelithiasis or bowel disease.

Bacterial sepsis is a common complication in patients having continual hemodialysis and is estimated to occur at a rate of 0.15 episodes per patient-dialysis-year.[15,16] Infection at the vascular access site appears to be the most common source of the bacteremia.[15,16] Staphylococci account for approximately 75 percent of access-related septicemia, while Gram-negative organisms and streptococci account for the remainder.[15]

In a recent study of hemodialysis patients, nearly a fourth of patients with chronic renal failure and bacteremia had no identifiable source of infection.[16] In our patient, we can only postulate that transient subclinical bacteremia during hemodialysis may have seeded the hepatic cyst that eventually required drainage.

With the widespread availability of dialysis modalities, patients with polycystic kidney disease have begun to enjoy longer survival. Infectious complications in these patients will likely become more frequent as longevity increases. We would advise that the differential diagnosis of septicemia in PKD patients be expanded to include liver cyst infection. While this is a serious complication, surgical intervention and antibiotic therapy can be curative.

REFERENCES

1. Hartnett M, Bennett W: Extrarenal manifestations of cystic kidney disease, *In* Gardner KD (Ed): Cystic Diseases of the Kidney. New York, John Wiley, 1976, p 203

2. Milutinovic J, Fialkow RJ, Rudd TG, et al: Liver cysts in patients with autosomal dominant polycystic kidney disease. Am J Med 1980; 68:741-744

3. Campbell GS, Bick HD, Paulsen EP, et al: Bleeding esophageal varices with polycystic liver: Report of three cases. N Engl J Med 1958; 259:904-910

4. DelGuercio E, Greco J, Kim KE, et al: Esophageal varices in adult patients with polycystic kidney and liver disease. N Engl J Med 1973; 289:678-679

5. Katzen NG: Fatal hepatic polycystic disease. Br Med J 1964; 1:839-840

6. Clinicopathological Conference: A case of polycystic disease of the liver and kidneys. Br Med J 1965; 4:1356-1358

7. Bennett AH, Stewart W, Lazarus JN: Bilateral nephrectomy in patients with polycystic renal disease. Surg Gynecol Obstet 1973; 137:819-820

8. Thakur ML, Coleman RE, Welch MJ: Indium-111-labeled leukocytes for the localization of abscesses: Preparation, analysis,

tissue distribution, and comparison with gallium-67 citrate in dogs. J Lab Clin Med 1977 Jan; 89:217-228

9. McDougall IR, Baumert JE, Lantieri RL: Evaluation of ^{111}In leukocyte whole body scanning. Am J Roentgenol 1979 Nov; 133: 849-854

10. McNamara JJ: Pyelonephritis in polycystic kidney disease. Am J Surg 1965; 109:178-181

11. Rothermel FJ, Miller FJ, Sanford E, et al: Clinical and radiographic findings of focally infected polycystic kidneys. Urology 1977; 9:580-585

12. Sweet R, Keane WF: Perinephric abscess in patients with polycystic kidney disease undergoing chronic hemodialysis. Nephron 1979; 23:237-240

13. Coleman RE, Black RE, Welch DM, et al: Indium-111 labeled leukocytes in the evaluation of suspected abdominal abscesses. Am J Surg 1980; 139:99-104

14. Fawcett HD, Lantieri RL, Frankel A, et al: Differentiating hepatic abscess from tumor: Combined ^{111}In white blood cell ^{99m}Tc liver scans. Am J Roentgenol 1980; 135:53-56

15. Dobkin JF, Miller MH, Steigbigel MD: Septicemia in patients on chronic hemodialysis. Ann Intern Med 1978; 88:28-33

16. Nsouli KA, Lazarus JM, Schoenbaum SC, et al: Bacteremic infection in hemodialysis. Arch Intern Med 1979 Nov; 139:1255-1258

Refer to: Edwards CQ, Cannon RB, Haug PJ, et al: Control of diabetes during pregnancy using continuous insulin infusion. West J Med 136:249-251, Mar 1982

Control of Diabetes During Pregnancy Using Continuous Insulin Infusion

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POOR CONTROL of diabetes during pregnancy is fraught with increased risk of complications in both mother and fetus.[1,2] Good control of diabetes reduces the rate of occurrence of complications.[3] Continuous subcutaneous insulin infusion (CSII) by pump is a way to maintain serum glucose at near-normal levels in nonpregnant diabetic patients.[4] Plasma glucose can be maintained at near-normal levels with intravenous insulin infusions during childbirth and this reduces complications in the mother and in the newborn.[5] Home monitoring of blood glucose during pregnancy helps the patient achieve normoglycemia.[6] However, we know of no other detailed reports about the usefulness of concurrent CSII and home monitoring of glucose in controlling diabetes during several months of pregnancy.

ABBREVIATION USED IN TEXT

CSII = continuous subcutaneous insulin infusion

The purpose of this paper is to report the effectiveness and practicality of diabetes control in pregnancy using CSII and home glucose monitoring. We studied two high-risk pregnant diabetic women during the last 15 and 23 weeks of pregnancy, respectively. Glucose control was better in both women while using CSII than with previous treatment regimens. Though some diabetic complications developed in the patients, each was delivered of a small baby near term.

Patients, Materials and Methods

After informed discussion and consent, glucose control was studied with continuous subcutaneous insulin infusion and home monitoring of blood glucose in two diabetic women during the final 15 and 23 weeks of their pregnancies, respectively. Patient information is presented in Table 1. Serum glucose control was poor in each woman before and during early pregnancy. Patient 1 had proliferative retinopathy and was classified as having White class R diabetes.[7] Before beginning CSII therapy, she had fasting and random glucose concentrations of 300 to 400 mg per dl. She also had frequent insulin reactions. Her glucose control remained very difficult even when multiple insulin injections were given each day. Patient 2 had systolic and diastolic hypertension and was classified as having class D_5 diabetes. She had fasting serum glucose levels of 192 to 293 mg per dl and 4 PM glucose levels of 189 to 488 mg per dl despite exercise, adherence to diet and three insulin injections per day before the CSII therapy was begun. Other complications in these two patients are listed in Table 1.

Continuous subcutaneous insulin infusion was by a portable battery-powered pump (Model AS2C, Auto Syringe, Inc., Hooksett, New Hampshire). Insulin was infused at a constant basal rate; preprandial pulses of insulin were infused as needed. Subcutaneous catheters from infusion pumps were changed at two- to four-day intervals.

Finger-prick blood dropped onto glucose-

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oxidase reagent strips (Dextrostix, Ames Co., Elkhart, Indiana) was used to determine serum glucose concentration two to four times a day in a portable colorimetric reflectance meter (Eyetone, Ames Co.). The patients recorded the results of all blood tests. Changes in insulin dosage were based on the blood glucose values recorded by the patients. The status of the patients and results of the self-testings were evaluated at weekly intervals by a physician.

Serum glucose levels (one to four times a month) were determined in the hospital laboratory as an independent measure of diabetic control. We found that 34 blood glucose measurements by patients using reflectance meters correlated well with simultaneous laboratory determinations ($r = 0.94$, $P < .001$).

TABLE 1.—*Profiles of Two Pregnant Women Using Continuous Subcutaneous Insulin Infusion (CSII) to Control Diabetes*

	Patient 1	Patient 2
Age	26	21
Duration of diabetes (years)	19	12
Hospital admissions for DKA	0	13
Previous pregnancies	0	2
Stillbirths	..	1
Toxemia	..	2
Complications of diabetes		
White classification[7]	R	D_6
Neuropathy		
Peripheral	+	−
Autonomic	+	−
Retinopathy	+	−
Nephropathy	−	−
Duration of CSII during pregnancy		
Weeks	23	15

DKA = diabetic ketoacidosis.

TABLE 2.—*Mean, Median and Standard Deviations of Serum Glucose Values While Fasting and at 4 PM by Month of Pregnancy During Continuous Subcutaneous Insulin Infusion*

		Patient 1			Patient 2		
		Mean	Median	SD	Mean	Median	SD
Month	Time	mg/dl			mg/dl		
4	Fasting	102	90	49			
	4 PM	119	100	74			
5	Fasting	115	115	57			
	4 PM	142	130	71			
6	Fasting	97	78	46	131	130	49
	4 PM	111	120	58	138	92	113
7	Fasting	139	135	55	178	169	57
	4 PM	122	105	57	140	132	59
8	Fasting	103	83	56	175	170	39
	4 PM	95	80	59	145	139	59
9	Fasting	103	105	18	137	135	39
	4 PM	120	120	34	117	121	55

Results

Blood glucose control was reasonably good in both patients during pregnancy using CSII therapy. Glucose concentrations determined while fasting and each day at 4 PM are shown in Table 2. Patient 1 determined her fasting glucose concentration 117 times and 4 PM glucose 111 times. Patient 2 determined her fasting glucose 107 times and 4 PM glucose 83 times.

Symptoms and signs of proved gastric autonomic neuropathy in patient 1 resolved after 2½ months of receiving CSII therapy. She was admitted to hospital once during the third trimester of her pregnancy for treatment of pyelonephritis. Her proliferative retinopathy advanced during pregnancy and laser therapy was required. At 37 weeks of gestation cesarean section was carried out because of preeclampsia. Her 2.8-kg infant aspirated amniotic fluid but went home with his mother five days after birth in good condition.

Patient 2 was treated with CSII during the last 15 weeks of pregnancy. Though her diabetes was controlled reasonably well (Table 2), she required two hospital admissions for treatment of toxemia. She was delivered of a 3.3-kg infant at 37 weeks of gestation. The infant had modest respiratory difficulty and jaundice but went home with his mother five days after birth.

No infections occurred at sites of subcutaneous catheter insertion. One pump failure occurred in the case of patient 1, which prevented her from receiving her small basal insulin dose one night. She resumed her schedule of basal and bolus insulin and her fasting and 4 PM glucose values the same day were 220 mg per dl and 70 mg per dl. The following day her fasting blood glucose value was 120 mg per dl. In no case did pump malfunction or incorrect reflectance meter reading cause an error in patient management decisions. Each patient achieved glucose control using CSII and home monitoring of blood glucose much better than during her many years of diabetes before CSII.

Patient 1 had eight blood glucose determinations that were less than 50 mg per dl. Patient 2 had ten blood glucose values of less than 50 mg per dl and recorded the sensation of insulin reaction on eight other occasions when her blood

glucose level was higher than 50 mg per dl or was not measured.

In both patients increased amounts of insulin were required during the last two months of pregnancy. Patient 1 used 80 to 90 units of insulin a day in the last two months of pregnancy, compared with 45 to 55 units before that time. Patient 2 required 60 to 70 units of insulin a day in the last two months, compared with a maximum of 50 units during the seventh month of pregnancy.

Comments

While diabetes is often difficult to manage during pregnancy, good control reduces maternal and fetal complications. Fetal mortality decreases from about 30 percent to 4.5 percent when maternal diabetes is well stabilized.[1-3,8,9] Very good control often requires a regimen of multiple injections of insulin each day.

In two high-risk diabetic women whose control was poor before starting CSII therapy, despite multiple daily insulin injections, we showed that CSII improved glucose regulation for the final 15 and 23 weeks of pregnancy. Because retinopathy or toxemia worsened in our patients, we must assume that CSII may not prevent the progression of certain complications. While more rigid regulation of blood glucose concentration (particularly in patient 2) might possibly have prevented toxemia, this is not necessarily so. Factors other than hyperglycemia are involved in the development of toxemia of pregnancy, some of which have not yet been elucidated.[10-12] It is encouraging that the gastric distention and retention, vomiting and diarrhea subsided in patient 1 after 2½ months of improved glucose control. There has been one report that motor-nerve conduction velocity improved after six weeks of good glucose regulation by CSII.[13]

Control of diabetes by CSII and frequent blood glucose monitoring at home require a lot of cooperation by both patient and physician. The patient must be conscientious and able to devote about half an hour a day to the mechanics of CSII, plus determining finger-prick blood glucose concentrations and keeping a record of results of all glucose determinations. The purchase price of the infusion pumps, reflectance meters and blood-glucose reagent strips was $1,150, $300 and 40 to 45 cents each, respectively (1980 prices).

We think home blood glucose monitoring is of great value in improving diabetic control whether or not an insulin infusion pump is used. We showed that it is feasible without major technical problems to teach high-risk pregnant women to manage insulin therapy by CSII, based on frequent home monitoring of blood glucose concentrations with a portable reflectance meter. This could likely be done from the time pregnancy is determined until delivery. If this were accomplished, maternal and fetal morbidity might be substantially reduced. We suggest that larger trials of CSII and home glucose monitoring be carried out throughout high-risk diabetic pregnancies to determine their impact on the prevalence and severity of maternal and fetal complications.

Summary

Two high-risk diabetic women were treated with continuous subcutaneous insulin infusion and self-monitoring of blood glucose levels for glucose regulation during the final 15 weeks of pregnancy in one patient and the final 23 weeks in the other. In both patients, control of glucose levels was better than when CSII was not used. Because diabetes during pregnancy increases risks to the mother and the fetus, good glucose control is desirable. Continuous subcutaneous insulin infusion and home monitoring of blood glucose concentration are practicable and can be used to improve diabetes control during high-risk pregnancies.

REFERENCES

1. Karlsson K, Kjellmer I: The outcome of diabetic pregnancies in relation to the mother's blood sugar level. Am J Obstet Gynecol 1972 Jan; 112:213-220

2. Kitzmiller JL, Cloherty JP, Younger MD, et al: Diabetic pregnancy and perinatal morbidity. Am J Obstet Gynecol 1978 Jul; 131:560-580

3. Leveno KJ, Hauth JC, Gilstrap LC, et al: Appraisal of "rigid" blood glucose control during pregnancy in the overtly diabetic woman. Am J Obstet Gynecol 1979 Dec; 135:853-862

4. Pickup JC, Keen H, Parsons JA, et al: Continuous subcutaneous insulin infusion: An approach to achieving normoglycaemia. Br Med J 1978 Jan; 1:204-207

5. Yeast JD, Porreco RP, Ginsberg HN: The use of continuous insulin infusion for the peripartum management of pregnant diabetic women. Am J Obstet Gynecol 1978 Aug; 131:861-864

6. Peacock I, Hunter JC, Walford S, et al: Self-monitoring of blood glucose in diabetic pregnancy. Br Med J 1979 Nov; 2:1333-1336

7. White P: Classification of obstetric diabetes. Am J Obstet Gynecol 1978 Jan; 130:228-230

8. Watkins PJ: Diabetes in pregnancy: A symposium—Diabetic control in pregnancy and labour. J R Soc Med 1978 Mar: 71:202-205

9. Essex NL, Pyke DA, Watkins PJ, et al: Diabetic pregnancy. Br Med J 1973 Oct; 4:89-94

10. De Alvarez RR: Preeclampsia, eclampsia and renal diseases in pregnancy. Clin Obstet Gynecol 1978 Sep; 21:881-905

11. Annat G, Raudrant D, Chappe J, et al: Maternal and fetal plasma renin and dopamine-beta-hydroxylase activities in toxemic pregnancy. Obstet Gynecol 1978 Aug; 52:219-224

12. Venuto RC, O'Dorisio T, Stein JH, et al: Uterine prostaglandin E secretion and uterine blood flow in the pregnant rabbit. J Clin Invest 1975 Jan; 55:193-197

13. Pietri A, Ehle AL, Raskin P: Changes in nerve conduction velocity after six weeks of glucoregulation with portable insulin infusion pumps. Diabetes 1980 Aug; 29:668-671

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Colonic Varices: An Unusual Source of Lower Gastrointestinal Hemorrhage

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PORTAL VENOUS HYPERTENSION from hepatic cirrhosis commonly leads to a dilation of submucosal venous channels in regions of the gastrointestinal tract where splanchnic and systemic veins anastomose.[1] Esophageal varices are clinically the most important and the most frequent portasystemic venous shunts occurring in patients with portal hypertension, these varices being frequently associated with spontaneous massive upper gastrointestinal hemorrhage. Rectal varices, mesenteric serosal varices, dilated paraumbilical veins (caput medusae) and spontaneous retroperitoneal splenorenal venous shunts likewise may develop in patients with substantial portal hypertension, but they are rarely associated with significant hemorrhage. Other regions of the gastrointestinal tract and abdomen, though subjected to the same high venous pressures, are rarely involved with significant hemorrhage from portal hypertension. We present the case of a patient with Laennec's cirrhosis in whom severe colonic hemorrhage developed from right colonic varices. This case illustrates the necessity of considering this entity in explaining substantial lower gastrointestinal hemorrhage in cirrhotic patients.

Report of a Case

A 35-year-old woman with a long history of alcohol abuse and Laennec's cirrhosis proved on biopsy was admitted with cramping right lower quadrant abdominal discomfort and the passage of multiple bright red bloody stools. Several years before admission she had an exploratory laparotomy; no appendectomy or bowel resection was done at that time. Four months before the present hospital admission she was admitted to another hospital with melena and rectal hemorrhage of bright red blood. Endoscopy at that time showed large nonbleeding esophageal varices and an active ulcer of the duodenal bulb. She was treated with antacids for peptic ulcer disease and did well over the next four months. She continued to consume up to a pint of alcohol a day, but stated that she did not have epigastric pain, melena, hematemesis or melanemesis during the four months before admission.

On the morning of admission she felt well except for mild cramping and lower abdominal discomfort and she spontaneously passed a large stool of clotted bright red blood. She then felt lightheaded and diaphoretic and vomited her breakfast. She stated she has never had hemorrhoids, colitis, altered bowel habits, diverticular disease or unknown bleeding disorders. On physical examination she was noted to be well developed, well nourished and somewhat older in appearance than her stated age. Blood pressure was 90/60 mm of mercury and pulse 124 beats per minute. Examination of the chest and heart showed no abnormalities. Her abdomen was nontender but did have a fluid wave and shifting dullness to percussion suggestive of ascites. The liver was palpable just beneath the right costal margin and had a 14-cm span to percussion. The splenic tip was also palpable. On rectal examination no obvious external hemorrhoids or palpable anorectal masses were found but there was bright red blood on the examining glove.

A sigmoidoscopy done to 20 cm showed fresh blood overlying normal mucosa without ulceration, mass lesions or rectal varices. There were no internal or external hemorrhoids. A nasogastric tube was passed soon after admission and returned clear yellow bilious fluid. Guaiac test of the nasogastric aspirate was negative. Her admission laboratory studies showed a hematocrit of 20 percent, a prothrombin time of 12.2 seconds (control 11.0 seconds), a partial thromboplastin time of 32.9 seconds, normal serum electrolytes, blood urea nitrogen and serum creatinine. Other laboratory test results included the following: serum albumin 2.7 grams per dl, serum total protein 5 grams per dl, serum total bilirubin 1.4

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mg per dl, serum aspartate aminotransferase (formerly serum glutamic oxaloacetic transaminase, SGOT) 37 IU per liter and alkaline phosphatase 81 IU per liter (normal <80). X-ray studies of the chest and plain films of the abdomen were normal.

Initially a transfusion with five units of packed red cells was carried out to maintain a hematocrit in the 30 percent range. Continued intermittent bright and dark red blood clots were passed through the rectum. At upper gastrointestinal endoscopy there were large esophageal varices extending into the cardia of the stomach. The gastric and duodenal mucosa was completely normal. Sequential scintigraphy with sodium pertechnetate Tc 99m and technetium Tc 99m sulfur colloid failed to show either ectopic gastric mucosa of a Meckel's diverticulum or extravasation of radionuclide into the bowel.

The patient's colon was lavaged clear by saline enemas and on the first hospital day a colonoscopy was done to the level of the midtransverse colon. The colonic mucosa was completely normal to the proximal transverse colon without evidence of diverticula, vascular malformations, dilated submucosal veins or mucosal erosions. Bright red blood was seen coming from the hepatic flexure into the transverse colon. Because of the large amount of blood coming from the hepatic flexure, the examination could not be extended to the ascending colon and cecum.

On the morning of the second hospital day, the patient underwent abdominal angiography while still hemorrhaging. The inferior and superior mesenteric arteries and celiac artery were selectively injected following transcatheter injection of 25 mg of tolazoline hydrochloride (Priscoline hydrochloride) to enhance the mesenteric venous views. Filming was carried out through the venous phase. No intraluminal extravasation of contrast material was shown, despite continued active hemorrhage requiring multiple blood transfusions during the study. Large dilated cecal and ascending colonic veins draining into a large right ovarian

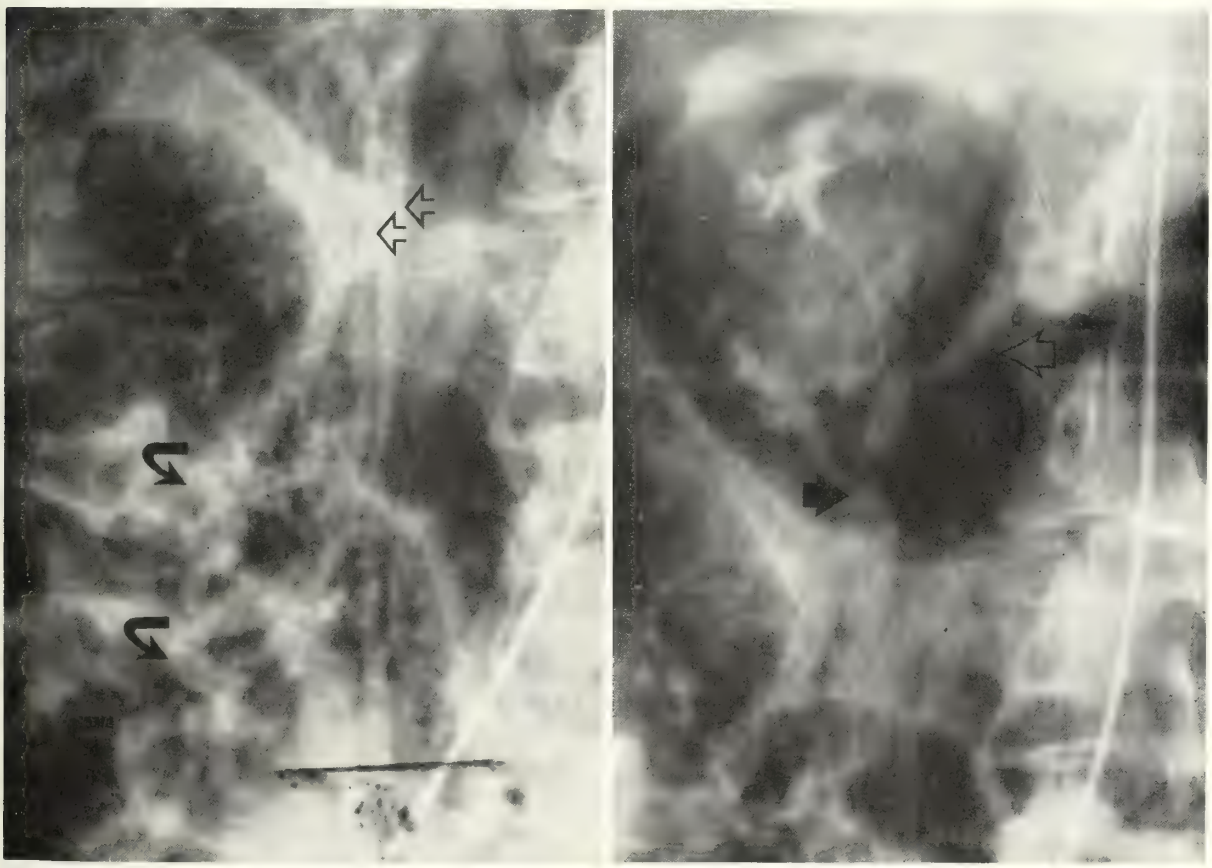

Figure 1.—Colonic varices. **Left,** early venous phase of superior mesenteric angiogram. Dilated tortuous veins (varices) (**curved arrows**) opacified in area of cecum. Double right ureter (**open arrows**) incidentally noted. **Right,** late venous phase. Dilated right ovarian vein (**solid arrow**) drains varices. The superior mesenteric vein (**open arrow**) is also opacified.

vein were identified, however (Figure 1). No other mesenteric varices were seen.

Active hemorrhage continued despite intravenously administered vasopressin, 0.4 units a minute. She required 12 units of packed red cells during the first 36 hours of hospital admission. At laparotomy, 48 hours after admission, a large cirrhotic liver was noted; a portal venous pressure of 46 cm of saline was measured (normal <20 cm of saline). An end-to-side portacaval shunt was made. Following the shunt procedure, the portal pressure was 21 cm of saline. The patient ceased hemorrhaging following portacaval shunting and had an uneventful postoperative course. She was discharged on the 14th postoperative day and remains well six months after surgery, without further rectal bleeding, anemia or guaiac-positive stool.

Discussion

Although fewer than 50 cases of mesenteric variceal hemorrhage mainly involving the colon have been reported in the English-language literature, this figure may underrepresent the true prevalence of this entity. In 110 cirrhotic patients undergoing percutaneous transhepatic portography, three demonstrated superior mesenteric while five had inferior mesenteric portasystemic shunts. Thus, 7.2 percent of all patients successfully studied by this technique had readily identifiable variceal shunts in proximity to the large bowel.[2]

Previous abdominal surgery in patients with portal hypertension may be an additional predisposing factor in the development of mesenteric varices at sites of adhesion of bowel to parietal peritoneal structures, such as scars and ostomy sites.[3]

The role of angiography is firmly established in diagnosing arterial hemorrhage from the lower gastrointestinal tract. Direct extravasation of contrast material from venous lesions such as varices is, however, rarely seen during angiography, even when vasoactive substances such as tolazoline are used.[4] One must rely on several criteria: exclusion of upper gastrointestinal source by negative results on endoscopy, failure to show arterial bleeding site angiographically during a time of active hemorrhage and visualization of the mesenteric varices with associated hepatofugal flow.[3-5] Transhepatic or transsplenic portography has, however, shown the actual extravasation of contrast material into the bowel.[6] The practical usage of this technique is limited not only by the lack of widespread availability but also by the prohibitive coagulopathy that makes deep-needle visceral punctures unacceptable in so many patients with cirrhosis.

Colonoscopy, though widely available, is unlikely to provide definitive diagnosis in patients who are bleeding vigorously from mesenteric varices. An unprepared colon filled with stool and clots is an unacceptable endoscopic field. In some patients, such as in the case presented, when hemorrhage ceases and multiple tap-water enemas successfully lavage the colon, limited or even complete colonoscopic examination may be able to confirm the varices while excluding mass lesions, small vascular ectasias and colitis.

Controversy exists over whether primary resection or portacaval shunting is the procedure of choice when patients fail to respond to medical therapy.[3,4,7] Four of five patients with hemorrhaging colonic varices now seen by one of the authors (M.P.F.) have responded successfully to portal venous decompression.[4] Although Moncure and associates[3] and Fee and co-workers[7] recommend resection of the varix-bearing bowel with delayed portasystemic shunt, primary portal decompression has several potential advantages. As with esophageal varices, rebleeding from colonic varices has not been a problem following successful portal decompression.[4] Resection of varix-bearing bowel, however, would be expected to carry with it a high rate of recurrence of bleeding similar to equivalent direct operations on esophageal varices. Also, with primary portal decompression, resection of unprepared bowel with its attendant morbidity is avoided. In our opinion, the advantages of shunt procedure outweigh the potential disadvantages such as encephalopathy and liver failure.

Summary

This is the report of a 35-year-old woman with known cirrhosis and esophageal varices in whom massive hematochezia developed requiring the transfusion of 12 units of blood. The venous phase angiography showed large cecal and ascending colonic varices draining into a right ovarian vein. The patient responded to portacaval shunt. Although infrequently reported as a source of lower gastrointestinal hemorrhage, up to 7 percent of patients with cirrhosis with portal hypertension may well have mesenteric varices concentrated mainly in the cecum. In the unprepared bowel, portal venous surgical decompression may well be preferred to colonic resection. In patients with

portal hypertension, this disease entity should be considered as another potential source of massive lower gastrointestinal hemorrhage.

REFERENCES

1. Edwards EA: Functional anatomy of the portasystemic communications. Arch Intern Med 1951 Aug; 88:137-154
2. Nunez D, Russel E, Yrizarry J, et al: Portasystemic communications studied by transhepatic portography. Radiology 1978 Apr; 127:75-79
3. Moncure AC, Waltman AC, Vandersaln TJ, et al: Gastrointestinal hemorrhage from adhesion-related mesenteric varices. Ann Surg 1976 Jan; 183:24-29
4. Federle M, Clark RA: Mesenteric varices: A source of mesosystemic shunts and gastrointestinal hemorrhage. Gastrointest Radiol 1979 Nov; 4:331-337
5. Hamlyn AN, Lunzer MR, Morris JS, et al: Portal hypertension with varices in unusual sites. Lancet 1974 Dec; 2:1531-1534
6. Kinkhabwala M, Mousavi A, Iyer S, et al: Bleeding ileal varicosity demonstrated by transhepatic portography. Am J Roentgenol 1977 Sep; 129:514-516
7. Fee HJ, Taylor JB, O'Connell TX: Bleeding intestinal varices associated with portal hypertension and previous abdominal surgery. Am Surg 1977 Nov; 43:760-762

Refer to: Pont A, Spratt D, Shinn JB: T_3 toxicosis due to nonmetastatic follicular carcinoma of the thyroid. West J Med 136:255-258, Mar 1982

T_3 Toxicosis Due to Nonmetastatic Follicular Carcinoma of the Thyroid

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IT IS UNCOMMON in American medical practice to encounter patients with massive goiters. The cause is rarely diligently researched and is often ascribed to iodine deficiency, inborn error of hormone synthesis or benign multinodular goiter. Therapy is usually offered for cosmetic purposes and includes either levothyroxine sodium or removal by surgery. The possibility that carcinoma constitutes all or part of the goiter may not be considered.

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Submitted, revised, May 18, 1981.

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ABBREVIATIONS USED IN TEXT

PTU = propylthiouracil
RIA = radioimmunoassay
T_3 = triiodothyronine
T_4 = thyroxine
TSH = thyroid-stimulating hormone

The recent influx of immigrants from Southeast Asia and Mexico includes many patients from "goiter belts." We recently encountered such a patient who had a massive goiter and clinical signs of hyperthyroidism. Laboratory evaluation confirmed triiodothyronine (T_3) toxicosis. The patient was presumed to have a multinodular goiter. Because she had moved from a low-iodine-intake to a high-iodine-intake area, the possibility that the hyperthyroidism was due to the jodbasedow effect was considered, albeit that jodbasedow usually results in a balanced hypersecretion of both thyroxine (T_4) and T_3.[1]

Surgical evaluation, however, showed the patient to have a massive follicular carcinoma of the thyroid. No evidence of metastasis was found. The case is presented to document the very rare occurrence of hyperthyroidism due to nonmetastatic follicular carcinoma of the thyroid. The occurrence of thyroid cancer in patients from "goiter" areas and the association of thyroid cancer with hyperthyroidism in general will be reviewed.

Report of a Case

A 52-year-old native-Mexican woman presented in October 1980 desiring cosmetic correction for a massive goiter (Figure 1). She had lived on the desert south of Guadalajara until moving to California six weeks before her clinic visit. She had noticed the swelling in her neck for about four years and felt that there had been some recent growth. She remembered that several other people in her community had had goiters.

The woman said she had not had dysphagia or respiratory problems, but that there had been mild weakness, fatigue, nervousness and heat intolerance. On physical examination the patient was noted to be anxious and moderately obese. Neither lid lag nor exophthalmos was present. Her skin was warm and smooth. There was no proximal muscle weakness, but tremor of the outstretched hands was evident. Blood pressure was 150/75 mm of mercury and pulse was 96 beats per minute. The thyroid gland was firm and

TABLE 1.—*Laboratory Values During Course of Treatment*

Date	Laboratory Values: T_4 Normal = 4.5-10.8 μg/dl μg/dl	Laboratory Values: RT3U Normal = 35-45% percent	Laboratory Values: T_3RIA Normal = 90-210 ng/dl ng/dl	Therapy
Day 1	5.4	31.1	302	None, begin PTU
3½ wk	5.3	33.2	239	PTU, 150 mg every 8 hr
6 wk	6.2	31.0	268	PTU, 150 mg every 8 hr
6½ wk	....	....	...	Subtotal thyroidectomy, discontinue PTU
7½ wk	7.9	35.6	110	None
2 mo	....	....	...	100 mCi ^{131}I
3 mo	10.0	37.1	143	None
4 mo	7.5	29.0	96	Levothyroxine sodium, 0.1 mg a day

T_4 = thyroxine; RT3U = resin triiodothyronine uptake; RIA = radioimmunoassay; PTU = propylthiouracil.

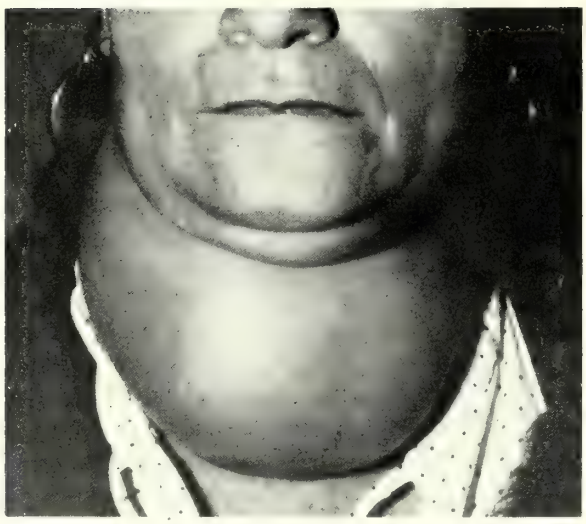

Figure 1.—A 52-year-old woman with massive goiter.

measured at least 15 by 10 by 5 cm. A to-and-fro bruit was audible at the right superior pole.

Results of the laboratory tests (Table 1) included a normal T_4 of 5.4 μg per dl (4.5 to 10.8 μg per dl) and a T_3 (by radioimmunoassay [RIA]) elevated at 300 ng per dl (90 to 210 ng per dl). Thyroid-stimulating hormone (TSH) was undetectable. Neither antimicrosomal nor antithyroglobulin antibodies were detected. A roentgenogram of the chest was normal, but plain films of the neck showed a large soft tissue mass with a central stellate calcification (Figure 2).

A presumptive diagnosis of colloid or multinodular goiter with T_3 toxicosis was made. No radioactive (iodine 123) scan was done as surgical removal had been chosen as the mode of therapy. The patient was begun on a regimen of propylthiouracil (PTU), 150 mg three times a day, and propranolol hydrochloride (Inderal), 10 mg four times a day. Although T_3 (RIA) remained mildly elevated, the patient was considered ade-

Figure 2.—Soft-tissue roentgenogram of the neck. Note central stellate calcification.

quately prepared for surgical procedure in November 1980.

At operation the surgeons resected a huge right thyroid lobe and half of a normal-appearing left thyroid lobe (Figure 3). The operation required five hours and was completed without incident. No lymphadenopathy was encountered and no frozen section was done. To our surprise, histologic examination showed the entire thyroid to be occupied by follicular cell carcinoma (Figure 4) extending to the line of resection of the left lobe. Capsular transgression and angioinvasion were present. Staining for amyloid was negative, as was immunofluorescent testing for calcitonin.

PTU administration was stopped the day of the surgical procedure. Eight days later, the results

of the T_4 and T_3 (RIA) were normal (Table 1). A 1 mCi iodine 131 scan of the remaining thyroid showed homogeneous uptake in the left lobe. Total body scan revealed no other areas of iodine concentration.

Due to a variety of socioeconomic and medical reasons, the patient chose to have an attempted ablation of the residual thyroid carcinoma with sodium iodide I 131. Three weeks after the surgical procedure, 100 mCi of ^{131}I was administered. Total body scanning two days later again showed iodine concentrating only in the region of the thyroid—that is, no evidence of distant metastases.

Three and a half weeks later, the patient was still chemically euthyroid, and levothyroxine sodium, 0.1 mg per day, was started. A month later, the results of both T_4 and T_3 (RIA) tests were normal (Table 1) and a higher suppressive dose of levothyroxine sodium was started.

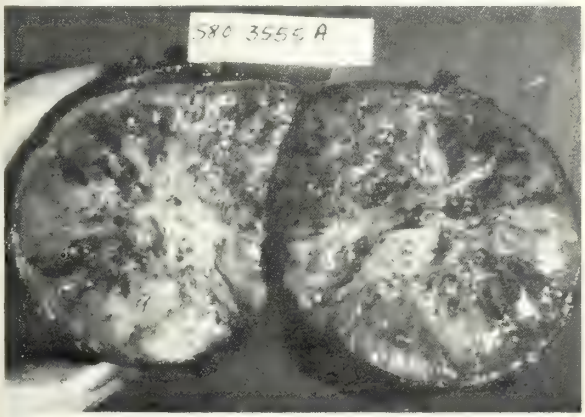

Figure 3.—Gross tissue specimen of resected right thyroid lobe. Note central calcification.

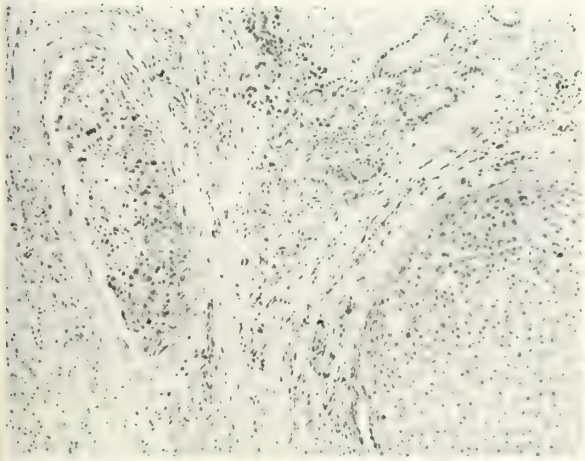

Figure 4.—Photomicrograph of follicular carcinoma of the thyroid. Note angioinvasion.

Methods

T_4, T_3 (RIA) and TSH determinations were all done in our laboratory by radioimmunoassay (Kallestad Laboratories, Inc., Austin, Texas). Triiodothyronine resin uptake (T_3RU) measurements were made with a kit from Nuclear Medical Laboratories, Inc., Dallas, Texas.

Discussion

In 1946 Leiter and colleagues[2] reported the first patient with hyperthyroidism due to functioning follicular carcinoma of the thyroid. Since then, approximately 35 such cases have been described. In 1964 Federman[3] reviewed the ten known cases and added three of his own. Aiyoshi and Ogata[4] summarized the 23 documented cases in 1978. An additional 11 cases have been presented in the literature since.[5-9] As follicular carcinoma generally lacks the thyroid hormone-synthesizing ability of normal thyroid tissue, a great bulk of tumor must be present before hyperthyroidism occurs. The 13 cases reviewed by Federman all had metastatic disease.[3] Of the 43 known cases, probably four have resulted from follicular carcinoma of the thyroid gland without evidence of distant metastasis. Sussman and associates[10] described one case in a 6-year-old child and Baumann and co-workers[5] reviewed three other cases with presumed thyroid confinement.

We cannot be certain that our patient has nonmetastatic disease. However, both the 1 mCi tracer dose and the 100 mCi therapeutic dose of ^{131}I resulted in uptake limited to the thyroid. Pathologic studies of the tissue specimen show follicular carcinoma extending to the resection line, and we presume that the residual left lobe is occupied by the tumor. Thus it would seem that the follicular carcinoma is the only source of thyroid hormone production. Even if metastatic lesions are present, they are probably nonfunctional. Our patient's tumor weighed 900 grams. Even if the cancer cells had a thyroid hormone secretory capacity that was 5 percent that of a normal thyroid, the equivalent of 45 grams of normal thyroid hormone secretory capacity would be present, which would be sufficient to render the patient hyperthyroid.

A case of T_3 toxicosis due to metastatic thyroid carcinoma was reported in 1973.[11] Kabadi and Albin[12] also described the case of a patient with metastatic follicular thyroid carcinoma who was euthyroid, but in whom there was preferential

secretion of T_3. That is, T_4 levels were low but T_3 and TSH values were normal.

To discuss why our patient manifested T_3 toxicosis would be speculative. However, it is interesting to consider the number of cases of hyperthyroidism due to metastatic follicular carcinoma that might have been detected had T_3 been measured in each patient.

There are numerous ways in which hyperthyroidism may be associated with cancer of the thyroid gland. Shimaoka and co-workers[13] described a case of hyperthyroidism and negligible ^{131}I uptake. The thyroid was later shown to be infiltrated by a malignant lymphoma and the hyperthyroidism was thought due to the lymphoma replacing normal follicles, causing a release of thyroid hormone into the circulation. Lindsay and Dailey[14] may have had a similar case in 1955. Hyperthyroidism from thyroid metastatic lesions of pancreatic adenocarcinoma[15] and breast adenocarcinoma[16] have also been described. Edmonds and Thompson[16] suggested that the release of thyroid hormone was not secondary to tumor replacing normal follicles, but was due to local effects of prostaglandins.

Graves' disease may coexist with thyroid carcinoma. Dobyns and co-workers[17] found that cancer and Graves' disease coexisted in less than 1 percent of their 32,000 cases. An incidence of 2.5 percent was found in surgical samples from the Armed Forces Institute of Pathology,[18] but both groups note that their incidence figures were subject to errors of selection. A simultaneous cancer incidence of as high as 22 percent has been reported in patients with Graves' disease and a cold nodule.[19] It remains uncertain whether there is any difference between the cancer incidence in patients with Graves' disease versus that of the normal population.[20] Similarly, no clear association between toxic nodular goiter and thyroid carcinoma exists.[17,18] The incidence of carcinoma in nontoxic nodular goiters is very low in North Americans,[21] but more data are needed on new immigrants.

Although the exact incidence is unavailable to us, it would seem that our patient came from a region in Mexico where goiters are common. Wahner and co-workers[22] have reviewed the incidence of thyroid carcinoma in the endemic goiter area of Cali, Colombia. Using matched sampling techniques, they found carcinoma to be 6.5 times more frequent in Cali than in New York. Numerous series have confirmed that thyroid carcinoma is more common in goiter belts and that follicular carcinoma may be more common than papillary carcinoma in these regions.[23,24] This contrasts dramatically with the thyroid cancer incidence in the United States, where papillary carcinoma is by far the most commonly encountered.[25]

Conclusion

This case report documents T_3 toxicosis due to follicular carcinoma confined to the thyroid gland. It is to be hoped that it will heighten suspicion of the possibility of thyroid carcinoma in people immigrating to this country from goiter belts.

REFERENCES

1. Vagenakis AG, Braverman LE: Adverse effects of iodides on thyroid function. Med Clin North Am 1975 Sep; 59:1075-1088
2. Leiter L, Seidlin SM, Marinelli LD, et al: Adenocarcinoma of the thyroid with hyperthyroidism and functional metastases—I. Studies with thiouracil and radioiodine. J Clin Endocrinol 1954 Nov; 14:1309-1320
3. Federman DD: Hyperthyroidism due to functioning metastatic carcinoma of the thyroid. Medicine 1964 May; 43:267-274
4. Aiyoshi Y, Ogata E: Report on a case of functioning thyroid carcinoma provoking thyrotoxicosis with review of literature. Endocrinol Jpn 1978 Dec; 25:623-629
5. Baumann K, Weitzel M, Bürgi H: Hormonproduzierendes Schilddrüsenkarzinom mit Hyperthyreose—Analyse von 6 Fällen und Übersicht über die Literatur. Schweiz Med Wochenschr 1979 Mar; 109:309-314
6. Citrin DL, Pederson J, Rose DP, et al: Radiation-induced carcinoma of the thyroid with severe thyrotoxicosis. Wis Med J 1978 Oct; 77:S97-99
7. Grayzel EF, Bennett B: Graves' disease, follicular thyroid carcinoma and functioning pulmonary metastases. Cancer 1979 May; 43:1885-1887
8. Snow MH, Davies T, Smith BR, et al: Thyroid stimulating antibodies and metastatic thyroid carcinoma. Clin Endocrinol (Oxf) 1979 Apr; 10:413-418
9. Cerletty JM, Listwan WJ: Hyperthyroidism due to functioning metastatic thyroid carcinoma. JAMA 1979 Jul; 242:269-270
10. Sussman L, Librik L, Clayton GW: Hyperthyroidism attributable to a hyperfunctioning thyroid carcinoma. J Pediatr 1968 Feb; 72:208-213
11. Sung LC, Cavalieri RR: T_3 toxicosis due to metastatic thyroid carcinoma. J Clin Endocrinol Metab 1973 Feb; 36:215-217
12. Kabadi UM, Albin J: T_3 euthyroidism in follicular thyroid carcinoma. Ann Intern Med 1978 Mar; 88:359-360
13. Shimaoka K, VanHerle AJ, Dindogru A: Thyrotoxicosis secondary to involvement of the thyroid with malignant lymphoma. J Clin Endocrinol Metab 1976 Jul; 43:64-68
14. Lindsay S, Dailey ME: Malignant lymphoma of the thyroid gland and its relationship to Hashimoto's disease: A clinical and pathologic study of 8 patients. J Clin Endocrinol Metab 1955 Nov; 15:1332-1353
15. Eriksson M, Ajmani SK, Mallette LE: Hyperthyroidism from thyroid metastasis of pancreatic adenocarcinoma. JAMA 1977 Sep; 238:1276-1278
16. Edmonds CJ, Thompson BD: Hyperthyroidism induced by secondary carcinoma in the thyroid. Clin Endocrinol (Oxf) 1978 May; 8:411-415
17. Dobyns BM, Sheline GE, Workman JB, et al: Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: A report of the cooperative thyrotoxicosis therapy follow-up study. J Clin Endocrinol Metab 1974 Jan; 38:976-998
18. Olen E, Klinck GH: Hyperthyroidism and thyroid cancer. Arch Pathol 1966 Jun; 81:531-535
19. Livadas D, Psarras A, Loutras DA: Malignant cold thyroid nodules in hyperthyroidism. Br J Surg 1976 Sep; 63:726-728
20. Reed JW, McCowen KD: Hyperthyroidism and thyroid cancer: A report of three cases. Postgrad Med 1980 Feb; 67: 169-172
21. Sokal JE: A longterm follow-up of nontoxic nodular goiter. Arch Intern Med 1957 Jan; 99:60-69
22. Wahner HW, Cuello C, Correa P, et al: Thyroid carcinoma in an endemic goiter area, Cali, Colombia. Am J Med 1966 Jan; 40:58-66
23. Cuello C, Correa P, Eisenberg H: Geographic pathology of thyroid carcinoma. Cancer 1969 Jan; 23:230-239
24. Heitz P, Moser H, Staub JJ: Thyroid cancer—A study of 573 thyroid tumors and 161 autopy cases observed over a thirty-year period. Cancer 1976 May; 37:2329-2337
25. Woolner LB, Beahrs OH, Black BM, et al: Classification and prognosis of thyroid carcinoma. Am J Surg 1961 Sep; 102: 354-386

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Cardiac Output and Function After Revascularization

TO THE EDITOR: I wish to express our appreciation of the thoughtful editorial by Califf and Rosati[1] in the October issue. It helps to place our paper[2] in the same issue in appropriate perspective.

I would, however, take issue with one point in their assessment of our community findings in relation to coronary artery bypass grafting. First, there is growing evidence that there is only a poor correlation between ejection fraction at rest and during strenuous exercise in patients with coronary heart disease. Second, we have follow-up invasive studies on nearly 50 patients in whom we have measured cardiac output by the direct Fick principle at graded levels of upright exercise up to symptom-limited exertion. Substantial changes in cardiac output, and therefore function, are observed in proportion to the adequacy of revascularization.[3] Hence, I need to caution about inferring that "the difference in survival is probably due to the better left ventricular function in the surgical patients [preoperative] rather than to the operation itself." The first reports of these findings appeared in the *British Heart Journal*[4] and in *Circulation*[5] which prompted us to seek and to obtain NHLBI funding for a more extensive study which is nearing completion.

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REFERENCES

1. Califf RM, Rosati RA: The doctor and the computer (Editorial). West J Med 1981 Oct; 135:321-322

2. Bruce RA, Hossack KF, Belanger L, et al: A computer terminal program to evaluate cardiovascular functional limits and estimate coronary event risks (Health Care Delivery). West J Med 1981 Oct; 135:342-350

3. Hossack KF, Bruce RA, Kusumi F, et al: Increased maximal cardiac output following bypass surgery. Cardiac Society of Aust & NZ, Mar 1981

4. Gey GO, Rudd T, Bruce RA: Improvement in exertional left ventricular dysfunction after revascularization. Br Heart J 1976 Oct; 38:1102-1104

5. Miller DW, Bruce RA, Dodge HT: Physiologic improvement following coronary artery bypass surgery. Circulation 1978; 57:831-835

The International System of Units (SI)

TO THE EDITOR: In our article on the International System of Units (SI)[1] in the December issue, we stated that Dr. William Barclay heads the Medical and Health Coordinating Group working on SI. Dr. Edward R. Powsner of Ingham Medical Center in Lansing, Michigan, has been elected chairman. In moving ahead with this effort, the group has agreed on the following:

The objective of the Medical and Health Coordinating Group (MHCG) is to provide the framework for working with appropriate individuals and organizations to expedite a uniform system of SI units in the various health sectors. The MHCG will provide guidance for all interested parties who desire to use the international (SI) metric system and to encourage consistent and proper applications of SI throughout the health field.

It will be interesting to observe the directions of the SI movement in the United States.

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REFERENCE

1. Bergeson PS, Smith EI: The international system of units (SI) and medicine. West J Med 1981 Dec; 135:526-529

Geriatric Medicine

TO THE EDITOR: This regards the December editorial "The Elderly as Interdependent Persons." Right on! Perhaps partly because of your "physical-psychological-social" triangles 32 years ago, I have developed two nonprofit housing projects for the elderly, assisted in formation of the University of San Francisco's gerontology program and learned about social interdependence in tens of thousands of thorough periodic checkups. As I read the December issue on Geriatric Medicine, I searched in vain for adequate recognition of such principles as, "the deepest principle of human nature is the craving to be appreciated" (William James), or "the cloistered controls had twice the mortality rate of those encouraged to help each other" (nursing home study) or "the 3 communities with large proportions of centenar-

ians had active, respected and productive niches for them" (*National Geographic,* 1972, approximately). That is, until your integrating editorial.[1]

The most graphic wisdom about geriatric medicine may be in the story of the man told "Your knee is not red, swollen, tender or unstable so it must be your age; after all, you're 103, Fred." "But, Doc, my other knee is also 103, and it don't hurt." The most important thing I learned from biostatistics was "Know your assumptions." You've heard about the statistician who drowned crossing a stream that *averaged* just one foot deep? Age should just alert us to a shift of probabilities. Respect requires individualization.

As the editorial so eloquently stated, "What appears to be needed is to further strengthen community and interpersonal action by the elderly. . . ." Is that not an application of the commandment, "Honor thy father and thy mother . . . that it may go well with thee"?

The chief problem of American elderly persons is *dis*-ease from condescension.

HOWARD F. LONG, MD, MPH
Pleasanton, California

REFERENCE

1. The elderly as interdependent persons (Editorial). West J Med 1981 Dec; 135:519

Language of Medical Diagnosis

To the Editor: Hats off to Dr. Weinberger![1,2] He has diagnosed a common condition—perversion of the language of medical diagnosis. This is most often encountered where, despite long-lived symptoms, no evidence of organic disease can be adduced. Reluctant to face foursquare and divulge the absence of organic disease, the physician applies a diagnostic euphemism. This lack of straightforward disclosure as to the nature of his malady leaves the patient to flounder indefinitely in his belief that what he has, no matter how vague and ill-defined, is "real," or "physical." The "kindly" physician has spared him the painful confrontation with the reality that his symptoms are psychogenic or "mental."

The failure to confront and disclose psychogenic symptoms for what they are abets chronicity and abuse in such disorders. It is "pure arrogance" for a physician to fail to disclose, in clear language, the probable nature of a disease to a comprehending patient.

FRED A. BAUGHMAN, JR, MD
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REFERENCES

1. Weinberger LM: Fibrositis (Correspondence). West J Med 1981 Nov; 135:425-426
2. Bennett RM: Author's reply to fibrositis (Correspondence). West J Med 1981 Nov; 135:426

Peptic Ulcer and Scapulocostal Syndrome

To the Editor: About 20 years ago, I discovered that peptic ulcer (or preulcer) disease may be a cause of the scapulocostal syndrome. This knowledge has helped me save many thousands of dollars for my patients. The scapulocostal syndrome is generally not well known, and peptic ulcer disease apparently has not been reported as one of the causes.

Scapulocostal syndrome on the left side may mimic myocardial infarction or angina pectoris with pain in the shoulder, neck, arm and chest in the fourth and fifth intercostal nerve areas. Women may also complain of breast pain and tenderness.

The scapulocostal syndrome characteristically has a trigger point at the upper medial angle of the scapula and tenderness over the fourth and fifth intercostal nerves on the involved side. There is frequently cervical muscle spasm with secondary headache suggesting tension headaches, greater occipital neuralgia, migraine or even brain tumor.

When the scapulocostal syndrome is secondary to peptic disease, anesthetizing the stomach with the ingestion of 10 to 15 ml of undiluted viscous xylocaine will soon result in considerable to complete relief of the pain, cervical myospasm and the tenderness of the fourth and fifth intercostal nerves and the trigger point. Treatment of the peptic syndrome will result in relief if no other coexisting causes are present. When due to peptic ulcer disease, the scapulocostal syndrome appears to occur more often on the left but may also be on the right or bilateral. Postural problems such as poor shoulder posture or a short leg may also cause the scapulocostal syndrome or may be coexistent causes and should be corrected.

NORMAN K. NOORDHOFF, MD
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Refer to: Rivin AU: 'Opening up' the health care system—Public protection and personal freedom (Commentary). West J Med 136:261-264, Mar 1982

Commentary

'Opening Up' the Health Care System

Public Protection and Personal Freedom

ARTHUR U. RIVIN, MD, *Santa Monica, California*

THE CALIFORNIA BOARD OF MEDICAL QUALITY ASSURANCE (BMQA) has recently rejected a proposal by the Public Affairs Research Group (PARG) titled "Public Regulation of Health Care in California."[1] The essence of the recommendation was "licensing by title," a system in which "anyone could be involved in health care for others" so long as he or she does not use titles reserved to licensed practitioners. For example, a self-proclaimed healer could not call himself physician, doctor or MD, but he could prescribe anything except "dangerous drugs" and carry out "very minor surgery."

But the issues raised in the report are not laid to rest. A special committee of the BMQA states that Section 2052, the present medical scope of practice code,[2] "needs substantial revision to reflect a more appropriate balance between the protection of the public and unnecessary limitation of individual freedom." This committee recommended a suggested model for revision of the legal definition of the practice of medicine. In their plan, medical practice would include only "prescribing dangerous drugs, performing surgery and using ionizing radiation." Commenting on this proposal,[3] Robert Rowland, executive director of the BMQA, said

> Instead of having the current law which says that doctors are the only ones who can do anything to anybody, and then having the other professions carve out their territory, we're saying let's identify those procedures or protocols that have clearly demonstrated danger to people that the state should regulate—and let's forget about the rest of it.

Dr. Rivin is Director of Medical Education, Santa Monica Hospital Medical Center, Santa Monica, California, and Clinical Professor of Medicine, University of California, Los Angeles, School of Medicine, Los Angeles.

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He added that

> if a proposal similar to this one was passed, there would be no reason to license the vast majority of currently licensed categories. Psychologists, registered nurses and physical therapists, for example, would not need to be regulated. We would basically have a fundamental reorientation of health manpower in the state.

To me the new proposal sounds as preposterous as the old one, inviting all kinds of untrained, nonscientific practitioners to exploit and probably harm a gullible public. Diagnosis, the fundamental basis for selecting the therapies described in the proposed model, would no longer be part of the legal definition of medical practice. Psychologic evaluation and treatment could be anyone's prerogative. "Nondangerous" drugs (what are they?) could be prescribed by anyone. Physical modalities of therapy would be left unlicensed and uncontrolled. The use of other nonionizing imaging methods (ultrasound, for example) would not be part of medical practice. Prenatal care and delivery would not be a concern of state licensing agencies.

Why did the BMQA commission the original study and why are they now exploring radical change? Why would numbers of recognized experts in nonmedical fields testify to the need for such a change? Why would the PARG, presumably careful thinkers, advocate the title licensure plan? I have searched the report and the quoted sources for answers. I quote directly key excerpts from the report and then list a summary of the report's reasons for recommending a change.

Key Report Passages

"The primary purpose of the change is to open up health care so that competent, qualified practitioners with a wide variety of skills and from

many different backgrounds can practice to the full extent of their knowledge and ability in the service of the people of California." Quoting Freidson,[4] and agreeing with his assessment, the report states

> something must be done to reorganize the rigid and unresponsive modes by which health care is provided. No matter what their capacities, physicians are not now doing their work properly. Reforms are necessary to bring more care to all segments of the population at a reasonable cost and to assure the quality of that care.

The report also states that

> Practice licensure perpetuates the existing system of health care, which grants some providers more power and authority than they merit, while wasting the talents and skills of others, stifling upward mobility and making turf conflicts inevitable. . . . the current statutory definition of the practice of medicine is the source of many of the most serious weaknesses in the existing system. It can be argued whether or not we are past the time when we can justify maintaining the dominance of physicians as a matter of public policy, but we are certainly past the time for it to be public policy that the definition of the practice of medicine should be synonymous with what physicians and physicians alone are authorized to do.

Summary Analysis of the Charges

These statements and others not directly quoted from the report indicate the charges that the reformers make and the problems that they seek to remedy.

1. The quality of care provided by MD's is not adequately assured.

2. Some aspects of health care are neglected or not provided by physicians and there are other practitioners who could fill those gaps. The people of California want and need other categories of health care providers and are denied their ministrations now because of state law.

3. People with lesser training (nurse practitioners, nurse midwives, pharmacists and so forth) also "practice medicine" of a kind and should be unfettered from state restrictions. They should be allowed "upward mobility."

4. We restrict personal freedom to choose by not allowing people to seek alternative practitioners under the misdemeanor threat of practicing medicine without a license.

5. Medical scientists do not have all the answers to health and disease.

6. Physicians are not making their services available to all the people. There is an accessibility problem.

7. The cost of physician care is unreasonable or beyond the reach of many people.

8. The medical schools are out of touch with the evolving needs and values of society and do not change their curricula appropriately.

9. "Turf fights" inevitably develop in health care and the BMQA should not have to bother with adjudicating them.

10. The key medical practice act, Section 2052, is outmoded and gives all MD's power, beyond their competence, to do licensed practice over the whole broad spectrum of medicine. The state provides physicians with a monopoly.

Critique of the Charges

In all of these charges the thoughtful physician would have to agree that there is some truth. I would like to examine each of them and then discuss the proposed reform.

1. *Assuring Quality of Physician Performance*

Although this matter is not directly relevant to the proposed scope of practice change, it is a part of a special attitude of discouragement and distrust of physicians to do their job well. Clearly there are incompetent physicians. There are also greedy physicians whose activities are more attuned to their bank balance than to their patient's welfare. There are also impaired physicians whose performance is not optimal. Although the relative numbers are small compared with the large number of competent and well motivated MD's, even one "bad actor" can cause great damage. The 1975 act setting up the BMQA has done a great deal to monitor, expose and restrict or delicense the incompetent. Those of us involved in hospital peer review committees and county medical societies can attest to a new action attitude to advise, reeducate or remove from practice the estimated 1 percent who are incompetent or fraudulent.

Yet the PARG report states that it is "questionable whether the board has significant impact on quality of care because . . . appropriateness of treatment . . . location and cost . . . facilities and technology . . . and knowledge and skills of practitioners are beyond the influence of the board." Not true! At least at the hospital peer review level, the knowledge, skills and appropriateness of treatment, even the location and cost, are and have been, within "the influence of the board." In the ambulatory care area it is certainly more difficult to monitor quality. The Family Practice Board, the American Society of Internal Medicine, in-

surance companies and others are actively working on this problem. One wonders how a BMQA dissatisfied with its control of physician quality performance and concerned with the obligation of the state to protect its citizens from the incompetence of the extensively trained, licensed and monitored physicians, can hope to reassure the public of quality of care by opening up the system to anyone who claims to be a healer and let him do as he wishes so long as it is not "surgery," prescribing "dangerous drugs" or using "ionizing radiation." What tortured reasoning is this?

2., 3. and 5. *Public Need for Other Kinds of Therapists and Expanded Roles*

What are these unmet health needs of the public? Physicians do not, indeed, have all the answers. Then who does? Are we talking about *holistic* practitioners, faith healers, laugh therapists, yin yang nutritionists or Laetrile advocates? Perhaps there is value in some of these activities. I am quite ready to concede that many physicians neglect the psychosocial and spiritual aspects of medical care. But all this is changing. The family practice movement emphasizes these matters in its training. More and more physician educational programs deal with the issues of ethics and human values. It seems ironic to me that now that medicine has reached a scientific base, when our most brilliant minds and millions of dollars are involved in carrying out human biological scientific research, we should now turn, as a matter of deliberate public policy, to encourage nonscientific practitioners.

It takes eight years for a drug to go through the various scientific steps from laboratory to marketing. The taxpayers spent $500,000 for the National Institutes of Health to investigate Laetrile, a drug that would not have made it past phase one of scientific trials, a drug that has bitterly disappointed many and greatly enriched others. Now shall the state of California encourage a "nutritionist," no matter how well meaning, to prescribe, say, ground plum pits instead of apricot pits, for cancer? Or shall we have large newspaper ads for powdered yak horn as an aphrodisiac?

In regard to expanding the role of other licensed practitioners, we are cautiously proceeding to do just that; sometimes, I grant, to the kicking, dragging and screaming of physicians. I do not doubt that some nurse practitioners I know would do as well for some of my office patients as I, and we need to explore their extended role as well as that of pharmacists, for example, whose talents and training are to a great degree wasted in ordinary drug stores. But let us do it carefully, with pilot programs and with advice and supervision of physicians who are, after all, the most highly trained and experienced people on whom society can call.

4. *Personal Freedom*

Democracy is a risky business. Freedom to choose is freedom to choose foolishly. Health care is too important for a *let the buyer beware* attitude. It is also too complex to expect even the most sophisticated and educated layman, and especially one who is desperately ill, to select the proper care from a smorgasbord of practitioners, without state control of educational requirements, licensing and monitoring of quality. Ethical considerations require informed consent. What would informed consent accomplish when a practitioner is himself uninformed? What would be the fate of the patient when the alternative practitioner, authorized by new laws to diagnose disease and to use an electric needle, recommends just burning off the little black mole that is, in fact, melanoma?

6. *Accessibility*

Doctors have not settled in remote rural areas or in inner cities. There are good reasons why they have not. This may change as the doctor surplus and the family practice movement grow. New communication, computer and transport technologies may help. The pertinent question is, how will the reform proposal alleviate the problem. It is interesting that nurse practitioners have not flocked to inner cities or rural areas either. What would the new breed of practitioner do to provide proper care in the ghetto or rural village?

7. *Cost*

How should society apportion its monetary rewards for goods or services? The question has interested philosophers and economists for centuries. Certainly the period of training, the relative value placed on the service, the seriousness of the responsibility and the hours of service should be part of the equation. I believe that in certain instances physicians' fees and incomes are too high. New practice systems, competition or insurance plans may change that. But what has the proposed reform plan to offer as corrective action? It is conceivable that the total cost of care

may go up with the advent of new scope of practice laws since physicians are not the only human beings plagued by greed or acquisitiveness. Diagnostic errors will certainly increase. For example, when anxiety, fatigue and weight loss have been treated for months by soothing massage and meditation, the physician may still have to treat for hyperthyroidism. Mistakes due to incompetence have a financial as well as a human cost.

8. *Unchanging Medical Curriculum*

I have just completed a term on a medical school curriculum committee. These are ponderous institutions with some rigid ideas and many professors convinced that their area deserves *prime time*. But they are changing, some more than others. In general there is more emphasis on patients' values and psychosocial matters. New departments of family practice are blossoming all over the country. General internal medicine training is replacing the previous overemphasis on subspecialization. Behavior modification and relaxation techniques have a spot on many teaching programs. Preventive health, nutrition, community health systems planning and coordinated team care are emerging. Some schools are even looking at Weed's[5] computer-assisted diagnosis and record keeping. This is real progress.

9. *Turf Fights*

Health care professionals will feud over who should do what to whom. The arguments may be high minded like "providing for the underserved," "preserving first class care," "freedom of choice" or "protecting the public welfare," but the claim on the dollar will be there as well. And while physicians and medical associations oppose the expansion of other health care people into "their territory," sometimes for selfish reasons, the chiropractors now pushing to be considered "primary care practitioners," and the podiatrists looking to operate farther up the leg are hardly acting out of ethical motivations or concern for the public welfare. This territory fight seems like just the place for government to decide whose training and standards best suit the public need.

10. *The Language of the Medical Practice Act*

If Section 2052 needs changing to accommodate other non-MD types of health practitioners or to restrict the scope of practice of MD's, then we should find a rational way to do that. While it may be burdensome and politically difficult for the BMQA, it is that agency's job to recommend to the legislature a scope of practice for each practitioner consistent with training, licensure and competence.

Conclusion

Scientific advances of the past 30 years have produced impressive improvements in health care. The appropriate pendulum swing away from too much emphasis on science and technology, and too little on self-care responsibility, the mind-body relationship and the ethical issues in medicine, is occurring now with our present licensing system. To advocate relaxation of licensure rules in the manner suggested because, in the words of the PARG report, it "might produce benefits not now clearly perceived" is both wishful thinking and dangerous.

Is the proper function of government to promote the general welfare and to do for people what they cannot do so well for themselves? Shall we strive to assure the public that their architects, bridge builders, airline pilots, teachers *and their health professionals* know what they are doing? If the answers are yes, than the legislature should license the best trained people to provide specific services and should monitor their continued competence. To propose excluding diagnosis from the legal definition of medical practice shows little understanding of what medical practice is all about.

REFERENCES

1. California Board of Quality Assurance Study: Public Regulation of Health Care Occupations in California. Public Affairs Research Group (PARG), 559 P Street, Sacramento, CA 95814, 1981

2. Medical Practice Act, State of California, 1937, revised 1975

3. Professional Regulation News. Published by ProForum, Inc., Vol 1, no. 3, Oct 1981

4. Freidson E: Professional Dominance. Chicago, Aldine, 1970, p 142

5. Weed LL: Physicians of the future (Sounding Board). N Engl J Med 1981 Apr 9; 304:903-907

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Ancient Technology in Contemporary Surgery

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Archaeologists have shown that ancient man developed the ability to produce cutting blades of an extreme degree of sharpness from volcanic glass. The finest of these prismatic blades were produced in Mesoamerica about 2,500 years ago. The technique of production of these blades was rediscovered 12 years ago by Dr. Don Crabtree, who suggested possible uses for the blades in modern surgery. Blades produced by Dr. Crabtree have been used in experimental microsurgery with excellent results. Animal experiments have shown the tensile strength of obsidian produced wounds to be equal to or greater than that of wounds produced by steel scalpels after 14 days of healing. We have been able to demonstrate neither flaking of glass blades into the wounds nor any foreign body reaction in healed wounds. Skin incisions in human patients have likewise healed well without complications.

The prismatic glass blade is infinitely sharper than a honed steel edge, and these blades can be produced in a wide variety of shapes and sizes. It is therefore suggested that this type of blade may find an appropriate use in special areas of modern surgery.

TWELVE YEARS AGO a technique was developed that allowed the manufacture of knife blades infinitely sharper than those in current surgical use. In these days of rapidly advancing technology, this fact might be of no more than passing interest. What is of interest, however, is the fact that this "new" technology of blade manufacture was but a rediscovery of a technique practiced up to 1 million years ago by ancient man. The material from which these blades were formed was stone. This article will attempt to trace the rediscovery of these remarkable cutting instruments, postulate ancient uses and perhaps suggest a place for this technology in the practice of contemporary surgery.

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History

We are all familiar with the stone instruments made for many centuries by cultures the world over before the availability of metals. These instruments range from the crude scrapers of 3 million years ago to exquisite spear points and arrowheads, which date from 14,000 years ago into the early 1900's in North America. Until very recently, many myths and mysteries have shrouded the method of manufacture of these artifacts. The first opportunity to learn sophisticated flint-knapping (the manufacture of tools

from stone) from a "stone-age man" came in 1911, when a starving Indian presented himself to civilization in Northern California.[1] Fortunately, he was befriended by Professors Waterman, Kroeber and Gibson of the University of California Anthropology Department, and his techniques of flint-knapping were carefully studied. During this same era, others were attempting to duplicate the varying ancient technologies that had produced different types of instruments in Northern America and elsewhere in the world.[2,3] Ishi, the last "wild Indian," died in the University of California Museum in San Francisco in 1916. Twenty years later, Professors Kroeber and Gibson had an assistant named Don Crabtree working in their lithic laboratory. He was pursuing an interest in lithic technology that began when he was a child collecting artifacts near his Southern Idaho home. Largely self-taught, he developed a skill in the art of flint-knapping which few have matched. His major contributions, however, were the result of his approach to this science and art. He became one of the world's primary authorities on experimental archaeology.[4] His scholarly study of stone artifacts proceeded through a logical deductive process to a rediscovery of the ancient techniques used to produce them. He was therefore able to duplicate for the first time many of the feats of ancient man. Indeed, Professor Bordes of Université de Bordeaux, suggested that American archaeology be divided into pre-Crabtree and post-Crabtree periods. Though Dr. Crabtree traveled widely in his later years, he maintained his residence near Kimberly, Idaho, and accomplished most of his experimental work in his home laboratory.

Despite the use of many natural materials and varying technology worldwide, the irregular flaked edge is the hallmark of those artifacts with which we are all familiar. There exists, however, an entirely different facet of lithic technology which is less well known. This technology consists of the ability to remove a long (up to 12-inch), extremely sharp blade from a core of obsidian (volcanic glass) in a single maneuver. The resulting blade is basically flat and triangular or trapezoidal in cross section (Figures 1 and 2). The glass blade can be produced in many shapes and sizes. These blades differ from the familiar spear point in that the cutting edge is absolutely straight, and is formed by a single fracture line. The two parallel cutting edges are extremely sharp, the edges themselves measuring approximately 30 angstroms in thickness. The comparison between this edge and that of a new razor blade is shown in Figure 3. At a magnification of 10,000 times, the razor blade edge appears essentially flat, whereas the edge of the glass blade remains a definite sharp angle. Similar types of blades, and the "cores" from which they were detached, have been found in archaeological sites in France dating back 35,000 to 1 million years.[5] This type of blade is also attributed to the Northwest Indians of North America, and was described by Ishi, the "wild Indian" of Northern California. The high point of this technology, producing thin pressure-flaked blades, was reached in Mesoamerica, where it was perfected approximately 2,500 years ago. These blades were described three centuries ago by the early Spaniards of Mexico and Guatemala. Indeed, there is mention of the Aztecs shaving the Spaniards with similar instruments.[6]

Figure 1.—Prismatic blades produced by Dr. Crabtree. Shown with obsidian "core" found in archaeologic site in Mesoamerica.

Stone artifacts of course do not deteriorate, and are found in abundance in the oldest archaeologic sites. Pottery is less durable, and bone even less so. Nonetheless, definite evidence for bone surgical procedures (amputation, trephination) has been discovered in Neolithic sites.[7,8] However, the form and condition of soft tissue at the time of death can only be a subject of conjecture years later. Therefore, though the availability in ancient times of instruments capable of soft tissue surgical operations is now well established, the uses to which these instruments were put can only be inferred. Undoubtedly, they were used for practical, religious and decorative purposes. There are many accounts of scarification among American Indians well into the last century. This practice is also widely distributed among the primitive tribes of the world today. Since the Aztecs (1,300

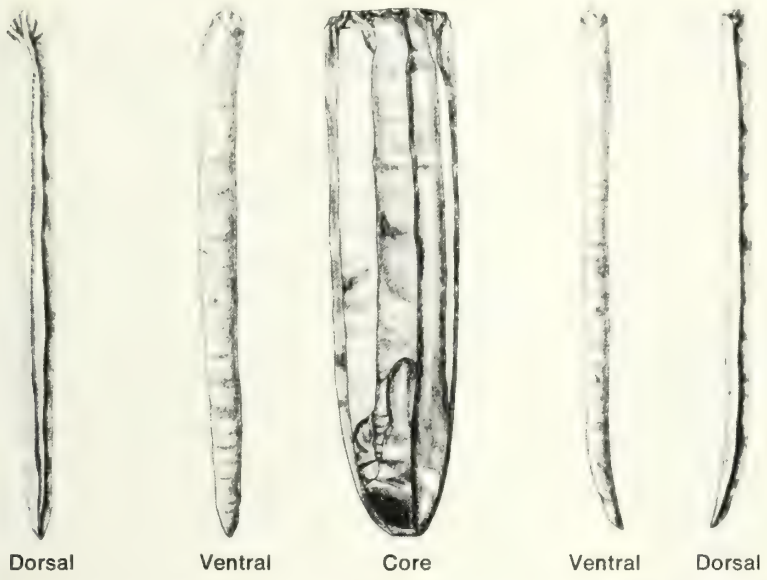

Figure 2.—Diagrammatic representation of obsidian "core," and blades produced from this core. (Courtesy Idaho State University.)

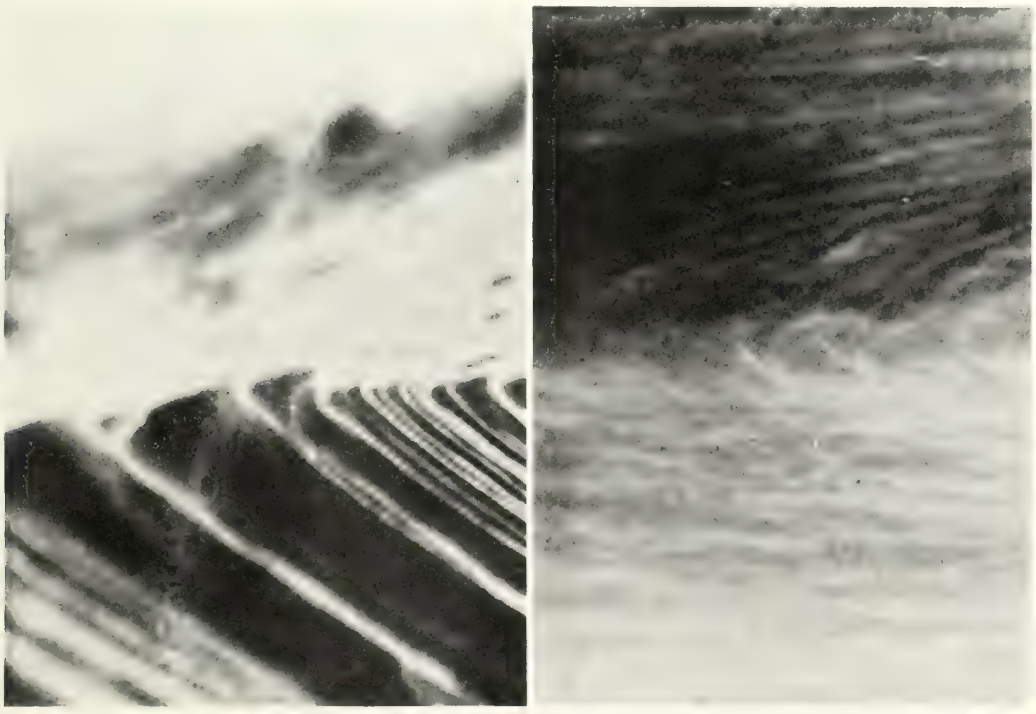

Figure 3.—Left, edge of prismatic glass blade. **Right,** edge of new stainless steel razor blade. Both edges are magnified 10,000 times by scanning electron microscope. (Courtesy of Anderson Pace.)

to 1,500 AD) are known to have possessed the finest obsidian instruments, and are also known to have practiced human sacrifice as a religious rite, it is probable that they used obsidian blades to accomplish the donor portion of the modern heart transplant procedure. Whether or not attempts at curative surgical procedures followed the availability of suitable instruments is, of course, difficult to prove. Ongoing studies by Semenov[9] may soon shed some light on this question. He and his co-workers have shown that obsidian knife edges are deformed microscopically in a predictable fashion, depending upon the type of material that has been cut by the blade. This microscopic "fingerprinting" of blades found in ancient sites may one day elucidate the purposes for which these knives were used.

Materials and Methods

The production of obsidian blades has been superbly described by Crabtree[10-14] and will not be detailed here. Meticulous preparation of an obsidian core is required, following which many blades can be produced in a relatively short time by a worker with the requisite skill. Dr. Crabtree produced blades up to 12 inches in length, and experimentally produced extremely fine microblades from obsidian, other lithic materials and many types of commercial glass.

Dr. Crabtree suggested in 1968 that modern surgeons might well look to glass blades for certain procedures.[15] He suggested, however, that "the surgeon who pioneers the use of such blades may be accused of reverting to caveman tactics." When faced with a surgical procedure himself in 1975, he convinced us to try an obsidian blade for the skin incision. Half of the incision was made with obsidian, and half with a standard No. 10 surgical scalpel. The obsidian knife was indeed sharper, and healing of the two extremities of the incision was identical. Several subsequent surgical procedures on physician volunteers scheduled for elective procedures have similarly produced normal healing and no complications. Because of the theoretic possibility of flaking of the stone blades, thereby leaving foreign material in the wound, these instruments have not been used on tissues other than skin and subcutaneous fat in humans in our institution.

In order to address the question of comparability of wound healing, several studies with experimental animals have been carried out. Our initial studies involved skin incisions, microvascular anastomoses and peripheral nerve incisions with prismatic glass blades. These procedures were carried out on anesthetized rabbits under 10 to 25 power magnification. The glass instruments did these functions admirably, and we could find no problems with wound healing in these animals.

A second group of experiments involved the examination of healed skin incisions made on the ventral surface of rabbits. A series of 2 to 3 cm incisions were made in such a way that there were paired longitudinal incisions equidistant from the ventral midline. Each pair of incisions was handled identically, with the only variable between the two being the cutting instrument. A No. 15 scalpel blade was used to produce one of the pair of incisions, and an obsidian blade to produce the other. Therefore, each animal served as its own control. The variables tested on individual pairs of incisions were staple closure, silk suture closure and subcutaneous hematoma at the time of closure. At 14 days the healed incisions appeared identical, and there were no clinical wound complications. The skin containing each incision was excised and then examined in two ways.

First, a 1 cm length of each healed wound was stressed by gradually applying a measured distracting tension to the wound. The applied force required to dehisce the obsidian-produced scars was 1.1 to 2.5 times that required for the scars produced by steel knives. These tests included incisions closed with each of the variables mentioned above.

Second, a portion of each healed wound was processed for examination of microscopic sections. All sections were evaluated in a blind fashion by a single pathologist. After 14 days of healing, all sections examined had a thin, well-organized scar. There was no evidence for included foreign body or foreign body reaction. The wounds produced by obsidian were indistinguishable from those produced by the honed steel edge after this healing period.

Discussion

The evolution of surgical instrumentation has always been of interest to those of us engaged in the field of surgery. Our concept of this evolution traditionally has been concerned with the period of time covered by recorded history, and therefore has concerned itself with the evolution of metal instruments. Archaeologists, however, have now shown us conclusively that stone cutting

blades of a quality equal to and surpassing that of steel blades in common usage today were available to ancient man up to a million years ago. The uses to which these remarkable blades were put is largely conjecture, since procedures upon soft tissue, animal and human, do not leave a record for us. However, there is direct evidence that such blades were used for ceremonial purposes (scarification) in North America, and that they were used for shaving in Mesoamerica. It does not seem unreasonable to assume that, during 1 million years of experimentation, these instruments might have been used to cut human tissue in an attempt to cure.

The recent advent of experimental archaeology has now provided us with the ability to reproduce products of the acme of ancient lithic arts. We once again have access to glass blades of infinite variety, and extreme sharpness. Though experimental work to date is limited, we feel that these blades, properly used, are safe for surgical procedures in humans.

In most fields of surgery, of course, a modicum of sharpness suffices, and one feels comfortable with the convenience of the modern disposable steel blade. However, in many specialized areas, scalpel blades and razor blades leave much to be desired. Examples that come to mind are the debridement of nerve ends for repair, microvascular surgery, fine plastic work on thin skin (blepharoplasty, for example) and ophthalmologic surgery. Though one with faith in modern technology cannot imagine that instruments equal to these various tasks cannot be produced today, the fact remains that no honed metal edge has matched that of the glass blade to date. Also, it is probable that production of prismatic glass blades, using minor modifications of ancient techniques, will be cheaper than the attempt at duplication of these cutting edges in steel. Our initial animal work in microscopic surgery with glass blades made by Dr. Crabtree leads us to feel that this is an area that should be further explored.

Conclusion

It is of historical interest to note that ancient man in several areas of the world had access to cutting blades of volcanic glass which were sharper than the surgical instruments of today. It is also postulated, though it has not yet been proved, that these instruments might have helped to initiate the field of surgical treatment. Experimental archaeology has shown us how to reproduce these blades, and initial animal experimention leads us to believe that they are safe in surgical use. In the near future it may be shown that there is a place in the modern surgical armamentarium for this descendant of ancient lithic technology.

REFERENCES

1. Kroeber T: Ishi in Two Worlds. Berkeley and Los Angeles, University of California Press, 1981

2. Wilson T: Arrowheads, spearheads and knives of prehistoric times. Report of US National Museum for 1897, 1899, pp 811-988

3. Holmes WH: Handbook of Aboriginal American Antiquities, Part I: Introductory—The Lithic Industries. Bur Am Ethnology Bull 1919; 60

4. Crabtree DE: Man's oldest craft revisited. Curator 1970; XIII: 179-198

5. Bordes F, Crabtree DE: The corbaic blade technique and other experiments. Tebiwa 1969; 12:1-21

6. McCurdy GG: The obsidian razor of the Aztecs. Am Anthropol 1900 Menasha; 2:417-421

7. Bick EM: The Classic Source Book of Orthopedics: Primitive Man and Ancient Practice. Clin Orthop 1979 Mar-Apr; 139: 2-16

8. Candis RF, et al: Prehistoric trephination of the frontal sinus. Ann Otol Rhinol Laryngol 1981; 90:186-189

9. Semenov SA: Prehistoric Technology. London, Cory, Adams and MacKay, Ltd, 1964, pp 13-15

10. Crabtree D: An Introduction to Flintworking. Pocatello, Idaho State University Press, 1972

11. Crabtree D, Butler D: Notes on experiments in flint-knapping—1: Heat treatment of silica materials. Tebiwa 1964; 7:1-6

12. Crabtree D: Notes on experiments in flint-knapping—3: The Flint-knapper's Raw Materials. Tebiwa 1967; 10:8-24

13. Crabtree D: A stoneworker's approach to analyzing and replicating the Lindenmeier folsom. Tebiwa 1966; 9:3-39

14. Crabtree D: Notes on experiments in flintknapping—4: Tools used for making flaked stone artifacts. Tebiwa 1967; 10:60-70

15. Crabtree D: Mesoamerican polyhedral cores and prismatic blades. Am Antiquity 1968; 33:446-478

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Information

A Program for Breast Cancer Detection

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THE AMERICAN CANCER SOCIETY'S 1980 statistics indicate that breast cancer will develop in 1 of 11 women (9 percent) sometime during her life.[1,2] The rate of early breast cancer detection is far below that which could be achieved, partly due to a prodigious amount of inaccurate publicity that has caused the average woman unwarranted fear of x-ray mammography.[3] In many cases this fear is a psychological shield against the apprehension that a tumor might be discovered. As a result, many women eventually come to their physicians with lesions that have been present for some time, and that have become quite large. These women mentally deny the presence of a mass, thus delaying diagnosis and treatment.

In our clinic, with its dedication to the early detection of breast disease, a history, physical examination and personalized instruction in breast self-examination are completed. An ultrasonic evaluation on a dedicated water-path breast scanner, only recently available for clinical use, is then done, followed by a xeromammographic study.

A primary contribution of our system is the psychological approach and its acceptance by patients. This important factor has received little or no attention in most of the scientific communications published regarding breast cancer.

A specially trained registered nurse individually assists each patient through the clinic. It has been shown in the Breast Cancer Detection Demonstration Projects study that a well-trained health practitioner can carry out a physical examination as effectively as a physician.[4]

As a woman proceeds through the clinic, she is first seated at a desk where an audiovisual device shows basic facts of her examination and how it will be done, emphasizing that she will experience no pain or discomfort. A history of factors shown to be important in breast carcinoma is then obtained. These factors will be taken into account by the radiologist who will interpret the study. The patient then goes to an examination room where she is asked to undress to the waist and to put her clothing and purse into a "take-along" basket so that she need not be concerned about her personal belongings.

The nurse doing the examination has been trained by a gynecologist. She examines the woman's breasts, records the findings and then gives instruction in self-examination. Each woman is given an illustrated pamphlet to refer to when she does her regular monthly self-examination. She may return at any time for reinstruction in breast self-examination at no additional cost.

Ultrasound mammography using dedicated ultrasound equipment is then carried out. The patient watches the television screen during the procedure to allay any anxiety. Ultrasound has become an accepted diagnostic tool. Many physicians lag behind, however, in knowledge of the newer applications.[5] Ultrasound mammography study has been found to surpass xeromammography in the differential diagnosis of both cystic and solid masses in young or dense breasts.[6]

A complete two-view or a single mediolateral oblique xeromammogram is then done on each breast. Upon completion of the x-ray studies, the woman is told that the results will be reported to her physician in a day or two. She may call the clinic if she has future questions (many do) and the nurse will answer where appropriate, or will refer her back to her regular physician.

Patients are accepted on a physician-referral basis rather than as "walk ins." It is important for a primary physician to continue follow-up on the patient, especially when the results are equivocal or lesions are detected that require treatment.

History

The history is used to identify risk factors for breast cancer.[7-9] The following increased risk fac-

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tors are noted in taking the patient's history: family history of breast cancer, especially of a grandmother, mother or sister; personal history of breast cancer; family or personal history of fibrocystic disease; onset of menopause after age 55; early onset of menses, that is, under age 11; childlessness; having first child after age 30, and ethnic background.

Physical Examination

Each nurse is required to spend a week in a training center where the ultrasound equipment is used daily and she is fully trained in its operation. She is trained in careful examination of the breasts and the use of appropriate terminology. The patients' acceptance of an empathic, well-trained registered nurse on a woman-to-woman basis is a primary and integral part of our approach. Patient acceptance has been high and this approach has presented no problem to the occasional male patients. The nurse clinician is responsible for detecting an abnormality and bringing it to the attention of the physician who will interpret the study and diagnose the patient's condition.

Instruction in Self-examination

A Gallup poll in 1979 showed that two thirds of the women polled had never had an examination of their breasts or been taught breast self-examination.[10]

Women coming to the clinic are afraid we may discover an abnormality. They are very relieved when their doctor informs them that no abnormalities have been found or that the mass palpated is a benign cyst. Although they are told it is possible that a small number of abnormalities may be missed, we have increased their awareness of breast cancer.

The nurse clinician carefully instructs women in modern methods of self-examination using mirrors at an appropriate height. It has been shown that most women, even after instruction, will examine themselves only several times a year or not at all. A greater number will examine themselves monthly after going through the clinic. The teaching is done with patience and understanding, stressing monthly examinations. A breast model (Betsy Breast) is used in which a woman learns to palpate four types of lesions. This allows her to test her newfound skills and to increase her awareness of breast lesions.

Ultrasound

We use the SMV 120™ Sonic Mammographic Viewer manufactured by Technicare, a subsidiary of the Johnson & Johnson Company.[11] This is a highly sophisticated computer-controlled ultrasonic breast scanning device. It has a high-resolution real-time water-path scanner specifically designed for breast imaging. The system is composed of three parts: a patient console and scanning tank, an electronic operating console and a physician image-viewing console.

The system is controlled by a microprocessor, which sequences the automatic operating functions. The operating console has numerous image-enhancing and data-manipulating features, including monitoring of patient and instrument status. The scanning tank has a dual flush/flash fill system, is chlorination controlled and has heating and filtering devices to maintain hygienic standards and patient comfort and safety.

Images are kept in a high-density memory device and can be displayed on a video monitor. The interpreting physicians thus have multiple images to review as they proceed in short increments through the breast. Any one of these images can be frozen, or the monitor can be run forward or backward; thus the physicians can review or create permanent film images of any selected area. This structuring of data is sophisticated and resolution is excellent for establishing a diagnosis. The breast can be scanned in three dimensions: sagittally, transversely and coronally. The A-mode histogram, which can be generated through any area of interest seen on the B-mode, is often very helpful in differentiating solid from cystic lesions. Its accuracy in differentiating cystic from solid masses in lesions 1 cm or larger is 100 percent.[12]

Mammography

We have been surprised by the number of lesions that show up on only one diagnostic device. Mammography is more reliable in patients with a large or fatty breast. In dense or dysplastic breasts (see Wolfe's classification) ultrasound is more effective.[13,14] Frazier[15] found that over 70 percent of cases in which xeromammogram studies gave false-negative findings were in the dysplastic or DY category. Negative-mode mammography is used on patients under 30 years to further decrease radiation.[16] Most important, lesions that are missed on mammography are usually picked up on the ultrasound, and the false-negative re-

sults of ultrasound are picked up by mammography.[15] We feel that using both devices picks up over 95 percent of lesions. However, we tell referring physicians that though we have tried to combine all methods to decrease the possibility of missing a lesion, it is still possible to miss a small lesion or to have false-positive or false-negative findings.

The works of Lundgren,[16] Libshitz[17] and Buchanan[18] and their co-workers suggest that single-view mammography may be used for screening. This reduces radiation exposure by 45 percent because the mediolateral requires more exposure than the craniocaudal view.[16-19] The small nests of calcifications indicative of a very small tumor are easily seen on the single-view mammogram, but are not shown by ultrasound. The mammogram and ultrasound are thus complementary. We are investigating the use of a single-view mammogram in conjunction with ultrasound.

Mammographic compression may help show a lesion but may also displace its apparent location. The ultrasound provides a more anatomic location of the lesion.

Our combined approach is cost effective because a single lesion found early can be treated inexpensively as opposed to the cost of extensive surgical procedure, radiation therapy and rehabilitative needs of the patient with advanced carcinoma. Equally important is the psychological impact on the patient, her life and the lives of those around her.

We would like to recommend this combined approach because it is a simple and relatively inexpensive method for the early detection of breast cancer. Early diagnosis greatly reduces the cost of treatment over that of continued care of breast cancer that has already metastasized by the time diagnosis is established. Patients treated for early breast cancer have an excellent prognosis. According to Lazlo Tabar of Fallun Hospital, Fallun, Sweden, the 20-year survival rate of patients treated for minimal breast cancer exceeds 90 percent.[20]

Our recommendations as to who should be evaluated are consistent with the 1979 combined statement on mammography of the American College of Obstetricians and Gynecologists and the American Cancer Society.[1,21,22] We agree with Frankl and Fleming[23] that the real hazard is not in carrying out but in not carrying out a potentially lifesaving examination.

Recommendations

First, all women over 35 should have a baseline examination. This should be repeated every one to three years, depending on breast type and risk factors, until the age of 50. Second, all women aged 50 and over should have annual physical, mammographic or ultrasound examinations. Finally, all women should be instructed in and encouraged to practice monthly self-examination.

Summary

A program is described for detecting breast cancer by the best currently approved methods, combined with a psychological approach to female patients that gains their cooperation and acceptance. Free-standing clinics have been created that accept patients by physician referral. On entering the clinic, the patient is met by a specially trained registered nurse who personally takes the patient through the clinic. The nurse takes a breast history, shows the patient a short, three-minute film explaining what she will experience in the clinic, and then does a complete breast examination. The patient is then instructed in supine and upright techniques of self-examination with the use of mirrors. She then applies her newly learned skills on a rubber breast model containing four specific lesions. A full examination of the breasts using computerized ultrasound is then done. Next, a low-dosage xeromammogram study is completed. Besides outstanding patient acceptance, the physician interpreting the films has the advantage of history, physical findings, ultrasound and xeromammograms for his review simultaneously. All these entities are complementary and proved effective—our success lies in their combination.

REFERENCES

1. American Cancer Society: Cancer Facts and Figures, 1981. New York, 1980, p 15

2. Brooks PG, Heldfond AJ, Margolin ML, et al: Graphic stress telethermometry—An ideal office screening device for the detection of breast disease. J Reprod Med 25:1-4, Jul 1980

3. Moskowitz M: How can we decrease breast cancer mortality? CA 30:272-277, 1980

4. Moskowitz M: Clinical examination of the breasts by nonphysicians—A viable screening option? Cancer 44:311-314, 1979

5. Janus CL, Janus SS: Ultrasound—State of the art. JCU 9: 217-218, 1981

6. Harper P, Kelly-Fry E: Ultrasound visualization of the breast in symptomatic patients. Radiology 137:465-469, 1980

7. Shapiro S, Strax P, Venet L, et al: The search for risk factors in breast cancer. Am J Public Health 58:820-835, May 1968

8. Schwartz GF: The clinical implications of risk factors in breast cancer. Nineteenth National Conference on Breast Cancer, 1981

9. Lyle KC: Female breast cancer: Distribution, risk factors, and effect of steroid contraception. Obstet Gynecol Surv 35:413-427, Jul 1980

10. Mahoney LJ, Bird BL, Cooke GM: Annual clinical examination—The best available screening test for breast cancer. N Engl J Med 301:315-316, Aug 9, 1979

11. Cole-Beuglet CM, Goldberg BB, Patchefsky AS, et al: Atlas of Breast Ultrasound. Sommerset, NJ, Technicare, 1980

12. Teixidor HS: The use of ultrasonography in the management of masses of the breast. Surg Gynecol Obstet 150:486-490, Apr 1980

13. Cole-Beuglet CM, Kurtz AB, Rubin CS, et al: Ultrasound mammography. Radiol Clin North Am 18:133-143, Apr 1980

14. Wolfe JN: Breast patterns as an index of risk for developing breast cancer. Am J Roentgenol 26:1130-1137, Jun 1976

15. Frazier TG, Ryan SM, Cole-Beuglet CM: Dysplastic Breasts by Mammography—Further Evaluation by Ultrasound, National Cancer Institute No. N01-CB-84273. US Dept of Health, Education, and Welfare, 1980

16. Lundgren B, Jakobsson S: Single view mammography: A simple and efficient approach to breast cancer screening. Cancer 38:1124-1129, Sep 1976

17. Libshitz HI, Fetouh SF, Isley J, et al: One-view mammographic screening? Radiology 120:719-722, Sep 1976

18. Buchanan JB, Joyer RM: Single-view negative mode xeromammography: An approach to reduce radiation exposure in breast cancer screening. Radiology 123:63-68, 1977

19. Andersson I, Hildell J, Mühlow A, et al: Number of projections in mammography: Influence on detection of breast diagnosis. AJR 130:349-351, Feb 1978

20. Wells C: Breast x-ray urged in routine exams. San Diego Evening Tribune, Mar 9, 1981

21. American College of Obstetricians and Gynecologists: Statement of Policy on Mammography. ACOG, 1979

22. Buchanan JB: Mammography advocated—District V ACOG: Convention Reporter 10:1,2, 1980

23. Fleming TC: Consensus on mammography: Ultimately, a majority of one (Editorial). Postgrad Med 67:23-26, Jun 1980

Refer to: Nanji AA, Freeman HJ, Anderson FH: Paralysis and rhabdomyolysis: A presenting feature of celiac disease (Information) West J Med 136:273-274, Mar 1982

Information

Paralysis and Rhabdomyolysis: A Presenting Feature of Celiac Disease

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RHABDOMYOLYSIS, seen in a wide variety of conditions,[1] is a rare complication of malabsorption.[2] We report a case of adult celiac disease in which paralysis and rhabdomyolysis, probably secondary to hypokalemia, were presenting features.

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TABLE 1.—*Serial Changes in Creatine Kinase (CK) After Admission*

Day After Admission	*CK IU Per Liter*	*Day After Admission*	*CK IU Per Liter*
0	13,000	12	1,860
2	11,200	15	478
4	8,000	18	112
7	4,560		

Report of a Case

A previously healthy 75-year-old Norwegian man was admitted to the Vancouver General Hospital with pronounced weakness of his arms and legs. He gave no history of diarrhea, loose stools, weight loss or drug intake.

On physical examination the patient's pulse was 110 per minute, blood pressure 130/70 mm of mercury and temperature 37.1°C. Examination of the cardiovascular and respiratory systems found no abnormalities. There was no clinical evidence of hepatomegaly or splenomegaly. Neurological examination showed generalized flaccid weakness with notably diminished tendon reflexes.

Laboratory studies showed a hemoglobin value of 12.8 grams per dl and a leukocyte count of 6,900 with a normal differential. Analysis of urine showed a 2+ hemoglobinuria with dipstick (Ames). This was later shown to be myoglobin.

Other laboratory studies gave the following values for serum: sodium 138 mEq, potassium 2.1 mEq, chloride 91 mEq, total carbon dioxide 32 mEq, creatine kinase 13,000 IU (normal, 15 to 100), lactate dehydrogenase 960 IU (normal, 90 to 210) and aspartate transaminase 105 IU per liter (normal, 5 to 35). Alkaline phosphatase was within normal ranges, as were urea nitrogen and creatinine.

Subsequent laboratory findings indicating malabsorption were as follows: plasma ionized calcium 1.5 mEq per dl (normal, 2.0 to 2.8), serum phosphorus 2.1 mg per dl (normal, 2.5 to 4.5), serum magnesium 1.6 mg per dl (normal, 1.8 to 2.8), serum folate 2.8 μg per liter (normal, 3 to 13) and serum B_{12} 140 ng per liter (160 to 925). Fecal fat excretion was 23.5 grams per 24 hours. Serial measurements of creatine kinase are shown in Table 1. An electrocardiogram showed the presence of atrial fibrillation. Radiologic examination of the small intestine showed dilated loops of bowel, segmentation and flocculation and a slow transit time suggestive of malabsorption. Jejunal biopsy was consistent with celiac disease, with

total villous atrophy. A bone biopsy showed the presence of osteomalacia.

Comment

The above case has a number of interesting features. The patient presented with paralysis and pronounced rhabdomyolysis which was probably secondary to hypokalemia. The potassium deficiency most likely resulted from malabsorption. This electrolyte abnormality in malabsorption is usually secondary to diarrhea.[2] However, our patient had no evidence of this.

It is recognized that chronic hypokalemia from any cause is associated with weakness, high serum muscle enzymes and histologic evidence of muscle necrosis.[3] The exact cause of muscle injury in hypokalemia, however, is not known. Changes in energy utilization, glycogen synthesis and electrolyte shifts have been suggested.[4] Another point of interest in this case was the presence of hypocalcemia without symptoms of neuromuscular irritability. This may have been due to the concomitant hypokalemia[5] which may have been even more severe than 2.1 mEq per liter because muscle damage is associated with potassium release. The alkaline phosphatase was normal despite the presence of osteomalacia. This has been described with celiac disease.[6]

REFERENCES

1. Rowland LP, Penn AS: Myoglobinuria. Med Clin N Am 1972 Nov; 56:1233-1256

2. Hertzmann EJ, Patterson JF, Stanley MM: Myoglobinuria and hypokalemia in regional enteritis. Arch Intern Med 1962 Jul; 110:117-124

3. Van Horn G, Drori JB, Schwartz FD: Hypokalemic myopathy and elevation of serum enzymes. Arch Neurol 1970 Apr; 22: 335-341

4. Knochel JP, Schlein EM: On the mechanism of rhabdomyolysis in postassium deficiency. J Clin Invest 1972 Jul; 51:1750-1758

5. Grossman RA, Hamilton RW, Morse BM, et al: Nontraumatic rhabdomyolysis and acute renal failure. N Engl J Med 1974 Oct 17; 291:807-811

6. Patterson CR: Hypocalcemia: Differential diagnosis and investigation. Ann Clin Biochem 1976 Jun; 13:578-585

Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions of general interest are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. Each is sent to members of the appropriate Scientific Advisory Panel.* Their responses are collated, reviewed and then submitted to the Quality Care Review Commission as the Scientific Board's opinion on the scientific and practice aspects of the question. The Commission adds suggestions to assist peer review units and authorizes publication.*

These opinions and positions are informational only and are not intended to be used as instructions, directives or policy statements. The appropriateness of care in individual cases should not be determined by these answers, but should be reviewed by local peer review committees.

Questions and reprint requests may be submitted to the Medical Practice Questions Committee, Quality Care Review Commission, California Medical Association, 731 Market Street, San Francisco, CA 94103.

Arthroscope Procedures

QUESTION:

Is it accepted medical practice to use an assistant surgeon for surgical procedures performed with an arthroscope?

OPINION:

It is the opinion of the Advisory Panel on Orthopedics that it is frequently necessary to have an assistant surgeon, particularly if an arthrotomy may be necessary.

The CMA Quality Care Review Commission comments further that "the use of assistant surgeons should not be considered a routine component of every arthroscope procedure."

Hyperbaric Oxygen Therapy

QUESTION:

What are the conditions for which hyperbaric oxygen therapy is considered acceptable medical treatment?

OPINION:

It is the opinion of the Advisory Panels on General Surgery, Dermatology, Occupational Medicine, Physical Medicine and Rehabilitation, Internal Medicine and Orthopedics that clearly proved uses for hyperbaric oxygen therapy are as follows:

- carbon monoxide poisoning,
- decompression sickness (the bends),
- gas embolism,
- gas gangrene due to *Clostridium perfringens*
- osteoradionecrosis,
- refractory osteomyelitis,
- cerebral edema,
- crush injury,
- Meleney's ulcer,
- compromised skin grafts,
- reimplantation of severed limbs,
- acute peripheral arterial insufficiency,
- acute traumatic peripheral ischemia,
- *Bacteroides* infections,
- central retinal artery insufficiency.

Stat-Tek Glucose Analyzer for Diabetes

QUESTION:

Is intermittent self-monitoring of blood glucose using the Stat-Tek glucose analyzer an acceptable practice for diabetes?

Dextrometer for Self-testing of Blood Glucose

QUESTION:

Is the use of—and purchase of—a Dextrometer for self-testing of blood glucose accepted medical practice for all diabetics, or should it be limited to certain patients and, if so, which ones?

OPINION:

It is the opinion of the Advisory Panels on General and Family Practice, Internal Medicine, Pathology and Pediatrics that home self-monitoring of blood glucose by diabetics can be an effective and acceptable means of stabilizing control of some patients having insulin-dependent diabetes, including pregnant diabetics and others for whom strict control should be achieved. Among the factors to be considered are (1) the motivation and reliability of the patient, (2) the need for periodic quality control checks and (3) cost of various home monitoring systems.

*The Scientific Board of the California Medical Association has a Scientific Advisory Panel for each of 24 recognized specialties of medical practice. Each Advisory Panel includes representation from the appropriate department of each of the eight medical schools in California, representatives of specialty societies in the field and representatives from the Specialty Sections of the Association. The Advisory Panels are thus broadly and authoritatively based in both academia and practice.

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NEW PROCARDIA® (NIFEDIPINE) *Capsules 10 mg*

Please see PROCARDIA® *prescribing information on next page.*

PROCARDIA® CAPSULES

For Oral Use

nifedipine

DESCRIPTION: PROCARDIA (nifedipine) is an antianginal drug belonging to a new class of pharmacological agents, the calcium channel blockers. Nifedipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, $C_{17}H_{18}N_2O_6$, and has the structural formula

Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 346.3. PROCARDIA CAPSULES are formulated as soft gelatin capsules for oral administration each containing 10 mg nifedipine.

CLINICAL PHARMACOLOGY: PROCARDIA (nifedipine) is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. PROCARDIA selectively inhibits calcium ion influx across the cell membrane of cardiac muscle and vascular smooth muscle without changing serum calcium concentrations.

Mechanism of Action: The precise means by which this inhibition relieves angina has not been fully determined, but includes at least the following two mechanisms:

1) Relaxation and prevention of coronary artery spasm: PROCARDIA dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of PROCARDIA in vasospastic (Prinzmetal's or variant) angina. Whether this effect plays any role in classical angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

2) Reduction of oxygen utilization: PROCARDIA regularly reduces arterial pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements and probably accounts for the effectiveness of PROCARDIA in chronic stable angina.

Pharmacokinetics and Metabolism: PROCARDIA is rapidly and fully absorbed after oral administration. The drug is detectable in serum 10 minutes after oral administration, and peak blood levels occur in approximately 30 minutes. It is highly bound by serum proteins. PROCARDIA is extensively converted to inactive metabolites and approximately 80% of PROCARDIA and metabolites are eliminated via the kidneys. The half-life of nifedipine in plasma is approximately two hours. There is no information on the effects of renal or hepatic impairment on excretion or metabolism of PROCARDIA.

Hemodynamics: Like other slow channel blockers, PROCARDIA exerts a negative inotropic effect on isolated myocardial tissue. This is rarely, if ever, seen in intact animals or man, probably because of reflex responses to its vasodilating effects. In man, PROCARDIA causes decreased peripheral vascular resistance and a fall in systolic and diastolic pressure, usually modest (5–10 mm Hg systolic), but sometimes larger. There is usually a small increase in heart rate, a reflex response to vasodilation. Measurements of cardiac function in patients with normal ventricular function have generally found a small increase in cardiac index without major effects on ejection fraction, left ventricular end diastolic pressure (LVEDP) or volume (LVEDV). In patients with impaired ventricular function, most acute studies have shown some increase in ejection fraction and reduction in left ventricular filling pressure.

Electrophysiologic Effects: Although, like other members of its class, PROCARDIA decreases sinoatrial node function and atrioventricular conduction in isolated myocardial preparations, such effects have not been seen in studies in intact animals or in man. In formal electrophysiologic studies, predominantly in patients with normal conduction systems, PROCARDIA has had no tendency to prolong atrioventricular conduction, prolong sinus node recovery time, or slow sinus rate.

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of PROCARDIA would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General. Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. See Warnings.

Peripheral edema. Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, ca should be taken to differentiate this peripheral edema from the effects of increasing left ventricul dysfunction.

Drug interactions: Beta-adrenergic blocking agents: See Indications and Warnings. Experienc in over 1400 patients in a non-comparative clinical trial has shown that concomitant administratic of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occ sional literature reports suggesting that the combination may increase the likelihood of congestiv heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there hav been no controlled studies to evaluate the antianginal effectiveness of this combination.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to ra for two years and was not shown to be carcinogenic. When given to rats prior to matin nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommend human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy category C. Nifedipine has been shown to be teratogenic in rats wh given in doses 30 times the maximum recommended human dose. Nifedipine was embryoto (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fet deaths, decreased neonatal survival) in rats, mice and rabbits at doses of from 3 to 10 times t maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximu recommended human dose resulted in small placentas and underdeveloped chorionic villi rats, doses three times the maximum human dose and higher caused prolongation of pregnan There are no adequate and well-controlled studies in pregnant women. PROCARDIA should used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: In multiple-dose U.S. and foreign-controlled studies in which adver reactions were reported spontaneously, adverse effects were frequent but generally not serio and rarely required discontinuation of therapy or dosage adjustment. Most were expected cons quences of the vasodilator effects of PROCARDIA.

Adverse Effect	PROCARDIA (%) (N = 226)	Placebo (%) (N = 23
Dizziness, light-headedness, giddiness	27	15
Flushing, heat sensation	25	5
Headache	23	20
Weakness	12	10
Nausea, heartburn	11	8
Muscle cramps, tremor	8	3
Peripheral edema	7	1
Nervousness, mood changes	7	4
Palpitation	7	5
Dyspnea, cough, wheezing	6	3
Nasal congestion, sore throat	6	8

There is also a large uncontrolled experience in over 2100 patients in the United States. Most the patients had vasospastic or resistant angina pectoris, and about half had concomitant tre ment with beta-adrenergic blocking agents. The most common adverse events were the sa ones seen in the controlled trials, with dizziness or light-headedness, peripheral edema, nausa weakness, headache and flushing each occurring in about 10% of patients, transient hypotensi in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not re with reduction in the dose of PROCARDIA or concomitant antianginal medication. Very rarely troduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly d to associated hypotension.

Several of these side effects appear to be dose related. Peripheral edema occurred in ab one in 25 patients at doses less than 60 mg per day and in about one patient in eight at 120 mg day or more. Transient hypotension, generally of mild to moderate severity and seldom requir discontinuation of therapy, occurred in one of 50 patients at less than 60 mg per day and in on 20 patients at 120 mg per day or more.

In addition, 2% or fewer of patients reported the following: **Respiratory:** Nasal and ch congestion, shortness of breath. **Gastrointestinal:** Diarrhea, constipation, cramps, flatulen **Musculoskeletal:** Inflammation, joint stiffness, muscle cramps. **CNS:** Shakiness, nervousne jitteriness, sleep disturbances, blurred vision, difficulties in balance. **Other:** Dermatitis, pruri urticaria, fever, sweating, chills, sexual difficulties.

In addition, more serious adverse events were observed, not readily distinguishable from natural history of the disease in these patients. It remains possible, however, that some or man these events were drug related. Myocardial infarction occurred in about 4% of patients congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduct disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving PROCARDIA with concomitant beta blocker th apy, the pattern and incidence of adverse experiences was not different from that of the en group of PROCARDIA treated patients (see **Precautions**).

In a subgroup of patients with a diagnosis of congestive heart failure as well as angina, d ness or light-headedness, peripheral edema, headache or flushing each occurred in one in e patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approxima one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occu in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one pat in 150.

Laboratory tests: Rare, mild to moderate, transient elevations of enzymes such as alka phosphatase, CK, LDH, SGOT, and SGPT have been noted, and a single incident of significa elevated transaminases and alkaline phosphatase was seen in a patient with a history of bladder disease after about eleven months of nifedipine therapy. The relationship PROCARDIA therapy is uncertain. These laboratory abnormalities have already been associ with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been repo twice in the extensive world literature.

OVERDOSAGE: Although there is no well documented experience with PROCARDIA overd age, available data suggest that gross overdosage could result in excessive peripheral vaso tion with subsequent marked and probably prolonged systemic hypotension. Clinically signifi hypotension due to PROCARDIA overdosage calls for active cardiovascular support inclu monitoring of cardiac and respiratory function, elevation of extremities, and attention to circula fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful storing vascular tone and blood pressure, provided that there is no contraindication to its Clearance of PROCARDIA would be expected to be prolonged in patients with impaired function. Since PROCARDIA is highly protein-bound, dialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION: The dosage of PROCARDIA needed to suppress gina and that can be tolerated by the patient must be established by titration. Exces doses can result in hypotension.

The starting dose is one 10 mg capsule, swallowed whole, 3 times/day. The usual effective range is 10–20 mg three times daily. Some patients, especially those with evidence of coro artery spasm, respond only to higher doses, more frequent administration, or both. In such tients, doses of 20–30 mg three or four times daily may be effective. Doses above 120 mg are rarely necessary. More than 180 mg per day is not recommended.

In most cases, PROCARDIA titration should proceed over a 7–14 day period so that the pl cian can assess the response to each dose level and monitor the blood pressure before proc ing to higher doses.

If symptoms so warrant, titration may proceed more rapidly provided that the patient is sessed frequently. Based on the patient's physical activity level, attack frequency, and sublin nitroglycerin consumption, the dose of PROCARDIA may be increased from 10 mg t.i.d. to 2 t.i.d. and then to 30 mg t.i.d. over a three-day period.

In hospitalized patients under close observation, the dose may be increased in 10 mg i ments over four to six-hour periods as required to control pain and arrhythmias due to ischem single dose should rarely exceed 30 mg.

No "rebound effect" has been observed upon discontinuation of PROCARDIA. However, i continuation of PROCARDIA is necessary, sound clinical practice suggests that the do should be decreased gradually with close physician supervision.

Co-Administration with Other Antianginal Drugs: Sublingual nitroglycerin may be take required for the control of acute manifestations of angina, particularly during PROCARDIA tion. See **Precautions, Drug Interactions** for information on co-administration of PROCA with beta blockers or long-acting nitrates.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contains 10 mg of nifedi PROCARDIA Capsules are supplied in amber glass bottles of 100 capsules (NDC 0069-2600

The capsules should be protected from light and moisture and stored at controlled temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

Issued January

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(Continued from Page 42)

PHYSICIANS WANTED

SPANISH-SPEAKING, PRIMARY CARE PHYSICIAN needed to join 2 MDs and 2 PAs at the Sea-Mar Community Health Center, a large multiservice center offering comprehensive care to Hispanics, Asian refugees and other local residents. Please contact Case Kolff, MD, 8720 14th Avenue South, Seattle, WA 98108, (206) 762-3730.

ORTHOPEDIC SURGEON—Board Certified or eligible, university trained orthopedic surgeon, preferably with additional specialty training (sports medicine, spine, joint replacement), to affiliate with an established orthopedic surgeon. Willing to wait for personable, experienced individual with commitment to patient care, research and teaching. New office building adjoining major hospital on the Palos Verdes Peninsula, California. Financial opportunity outstanding. Submit a CV and references to: James T. London, MD, 1360 West 6th St., Suite 305, San Pedro, CA 90732; (213) 833-2406.

WANTED—ALLERGIST—To open new practice in fast growing suburban area. No competition. Established professional bldg. across the street from large suburban hospital. Free rent for 6 months. Contact Richard Lomas, MD, 17800-A Talbot Rd. S., Renton, WA 98055.

HEMATOLOGIST-ONCOLOGIST WANTED—To join two others in well-established subspecialty practice in the Los Angeles area. Board certified or eligible. Excellent salary with unusual opportunity for early partnership. Inquiries and CV to Box 6282, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GENERAL PRACTITIONERS SPECIALISTS—Are you considering a practice change, please call us, let's talk. We have many opportunities in various West Coast locations. If you would like to join a group, associate or own your own practice we can help. Call us collect at (714) 997-0853, or send CV to Physicians Search Associates, 1201 W. La Veta, Suite No. 209, Orange, CA 92668.

PSYCHIATRIST WANTED for Bassett Army Hospital, Fort Wainwright, Alaska. Bassett Army Hospital is a fully equipped, 80-bed hospital supporting a military population of 6,500. Fort Wainwright is located adjacent to Fairbanks, Alaska. Excellent Opportunity for a fully trained psychiatrist. Guaranteed income, bonuses, and an excellent benefits package. Contact: Captain Pat Shipley, Bldg. 138, Room 116, Naval Support Activity (Sand Point), Seattle, WA 98115 or call (206) 527-3548.

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English/Spanish speaking. University trained in all procedures including ERCP, laparoscopy, manometry, etc. Currently Chief of GI Section in multispecialty clinic and hospital. Wish to relocate to California. Please reply to Box 6287, Western Journal of Medicine, 731 Market St., San Francisco, 94103.

FACULTY INTERNIST

Available July 1982. Full-time faculty position for a General Internist with a UCLA affiliated program located in Antelope Valley. Excellent salary and fringe benefits. Collegial atmosphere in a dynamic, successful program. Contact:

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PRACTICES AVAILABLE

ORTHOPEDISTS, INTERNISTS, FP/GP, OB/GYN, SURGEONS, PEDIATRICIANS, OPHTHALMOLOGISTS, OTHERS. For help in BUYING or SELLING a medical practice, medical building, or arranging an association contact Mary Bradshaw, 21 Altamount Dr., Orinda, CA 94563; (415) 376-0762. Consulting, appraising, partnerships, placement.

SITUATIONS WANTED

INTERNIST with young family seeks job-sharing or part-time private association. Desire California suburban to semi-rural area. Write Box 6267, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

UNIVERSITY CARDIOLOGIST seeks group practice including EP and Cath. Experienced invasive and noninvasive, including ZD. Reply to Box 6278, The Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

INTERNIST (BC)—With Allergy-Immunology subspecialty (BE) desires practice opportunity in So. Calif. Prefer IM emphasis with opportunity to do some allergy. Well trained in inpatient and outpatient care. Available July, 1982. Reply to Box 6282, The Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

RADIOLOGIST—Desires locums or permanent position. Contact Anthony Cassens, MD, 2669 Ardshead Dr., La Habra, CA 90631, (213) 691-1501.

WANTED: Univ. trained general surgeon to join two other general surgeons in 13-physician clinic. Excellent qualifications required. Location: southern Idaho, near excellent outdoor recreation. Write Box 1233, Twin Falls, ID 83301.

PULMONOLOGIST, 35, seeks opportunity in private practice in S.F. Bay Area, July 1982. Prefer mixture of in-pt and out-pt practice; group, association or solo. Currently on pulmonary faculty and Director of Medical ICU at major university. Previous experience in consultative internal medicine private practice. Reply to Box 6281, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ORTHOPEDIC SURGEON. Age 69. Board certified. Interested in office orthopedics and/or disability examinations. Apply Box 6225, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PEDIATRICIAN—California license. 47. Had private practice for 16 yrs. Desires to work for regular hours job, HMO, outpatient clinics, ambulatory, student health, no night calls. Preferably in San Francisco Bay Area or Southern California. Contact Box 6283, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GENERAL, PERIPHERAL VASCULAR, SURGEON. ABS, FACS. 5 years intensive surgical practice Northern California wishes to relocate in Southern California, Orange County or San Diego area. U.S. university trained with fellowship, U.S. born. Also experience academic medicine. Reply Box 6255, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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Sunnyvale Medical Clinic
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Sunnyvale, CA 94086

ALCENAS HOSPITAL, Kirkland, Washington, member Comprehensive Care Corporation, seeking qualified physician full-time for June 1, 1982. Diagnosis and management of abstinence syndromes from alcohol and drugs, treatment of primary medical illnesses and complications of alcoholism and substance abuse, and supervision of medical aspects of rehabilitation. 82-bed hospital, staff of 3 MDs/2 Nurse Practitioners, Adolescent unit included. Team work with nurses and counselors. Opportunity for teaching and developing programs. Internist preferred with interest in adolescent medicine, nutrition and/or psychiatry helpful. For additional information please contact: **Sandra Counts, MD, Medical Director, ALCENAS HOSPITAL, 10322 N.E. 132nd, Kirkland, WA 98033.**

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LOCUM TENENS WANTED

FAMILY PHYSICIAN—Board certified, semi-retired wishes part-time position in vicinity San Diego, San Jose or Phoenix. Available July 1, 1982. Reply Box 6264, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGIST seeks locum tenens work. Contact Box 6274, The Western Journal of Medicine, 731 Market Street, San Francisco, CA, 94103.

CONSCIENTIOUS YOUNG INTERNIST, University trained, seeks locum tenens in Internal Medicine in Bay Area. Available January through June, part or full time. Reply Box 6270, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

NEUROSURGEON—Northern California, needed for April 1982. Mainly for coverage of office practice and inpatient followup as well as handling emergency cases. Reply Box 6285, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact: **Carol Sweig, Director, 1124 Ballena Bl., Alameda, CA 94501. (415) 521-4110.**

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RENTON, WA, suburb of Seattle—Outstanding opportunity for practice of Internal Medicine. Office in established professional bldg., directly across from large city hospital, growing area. For details contact Richard Lomas, MD, 17800-A Talbot Rd., S., Renton, WA 98055.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

BREASTFEEDING—A Manual for Health Professionals—Victor LaCerva, MD, Clinical Assistant Professor, Department of Pediatrics, University of New Mexico Medical Center. Medical Examination Publishing Co., Inc., an Excerpta Medica Company, 969 Stewart Avenue, Garden City, New York (11530), 1981. 173 pages, $10.50 (paperback).

THE CLAY PEDESTAL—A Re-examination of the Doctor-Patient Relationship—Thomas Preston, MD, Director of Cardiology, U.S. Public Health Service Hospital, Seattle; Fellow of the American College of Cardiology; Fellow of the American Heart Association Council on Clinical Cardiology; Professor of Medicine, University of Washington. Madrona Publishers, Inc., 2116 Western Avenue, Seattle, WA (98121), 1981. 226 pages, $12.95.

CLINICAL CARDIOLOGY—Third Edition—Maurice Sokolow, MD, Professor of Medicine Emeritus, Senior staff member, Cardiovascular Research Institute, formerly Chief of Cardiology and Program Director of the USPHS Clinical Cardiology Training Program, University of California, San Francisco; and Malcolm B. McIlroy, MD, Professor of Medicine, Senior staff member, Cardiovascular Research Institute, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1981. 763 pages, $21.50 (paperback).

EPILEPSY: The Facts—Anthony Hopkins, Physician in Charge, Department of Neurological Sciences, St. Bartholomew's Hospital, London. Oxford University Press, 200 Madison Avenue, New York, NY (10016), 1981. 158 pages, $11.95.

GENERAL UROLOGY—Tenth Edition—Donald R. Smith, MD, Professor of Urology, University of California School of Medicine, San Francisco; Visiting Professor of Urology, University of Ain Shams, University of Cairo. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1981. 598 pages, $19.50 (paperback).

HEAD AND NECK ONCOLOGY—Edited by A. Robert Kagan, MD, Department of Radiation Therapy, Southern California Permanente Medical Group, Los Angeles; and John W. Miles, MD, Department of Otolaryngology, Southern California Permanente Medical Group, Los Angeles.—In the series: CONTROVERSIES IN CANCER TREATMENT, Harvey A. Gilbert, MD, Series Editor. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston, MA (02111), 1981. 360 pages, $55.00.

LAW ON CULTS—I. H. Rubenstein, member of the Illinois Bar. The Ordain Press, P.O. Box 68, Chicago, IL (60690), 1948, 1981. 120 pages, $4.95 (paperback).

LONGEVITY—Fulfilling Our Biological Potential—Kenneth R. Pelletier, PhD, Assistant Clinical Professor, Department of Psychiatry and the Langley Porter Neuropsychiatric Institute, University of California, San Francisco, School of Medicine; Assistant Professor, Department of Public Health, University of California, Berkeley, and Director of the Psychosomatic Medicine Clinic, Berkeley. A Merloyd Lawrence Book, Delacorte Press/Seymour Lawrence, 1 Dag Hammarskjold Plaza, New York, NY (10017), 1981. 431 pages, $15.95.

PERSONAL MONEY MANAGEMENT FOR PHYSICIANS—Third Edition—Edited by Lawrence Farber, Senior Editor, **Medical Economics** magazine. Medical Economics Books, Box 157, Florence, KY (41042), 1981. 253 pages, $19.95 (Price subject to change after Feb. 1, 1982).

PROGRESS IN PERINATAL NEUROLOGY—Volume 1—Edited by Rowena Korobkin, MD, Children's Hospital Medical Center, Oakland; and Christian Guilleminault, MD, Stanford Sleep Disorders Clinic and Research Center, Stanford University Medical School. Williams & Wilkins, 428 East Preston Street, Baltimore, MD (21202), 1981. 238 pages, $35.00.

RESPIRATORY MEDICINE AND INTENSIVE CARE FOR THE HOUSE OFFICER—John J. Marini, MD, Assistant Professor of Medicine, University of Washington, Seattle. Williams & Wilkins, 428 East Preston Street, Baltimore, MD (21202), 1981. 273 pages, $9.95 (paperback).

SOME CLASSICS OF EXPERIMENTAL ONCOLOGY—50 Selections, 1775-1965—Michael B. Shimkin, MD, University of California, San Diego School of Medicine, La Jolla. NIH Publication No. 80-2150, Oct. 1980. National Institutes of Health, USPHS, U.S. Department of Health and Human Services. For sale by the Superintendent of Documents, United States Government Printing Office, Washington, D.C. (20401). 739 pages, no price quoted.

SURGICAL ONCOLOGY—Edited by Theodore X. O'Connell, MD, Assistant Clinical Professor of Surgical Oncology, University of California, Los Angeles, School of Medicine; Surgical Oncologist, Kaiser-Permanente Medical Center, Los Angeles.—In the series: CONTROVERSIES IN CANCER TREATMENT, Harvey A. Gilbert, MD, Series Editor. G. K. Hall & Co., 70 Lincoln Street, Boston, MA (02111), 1981. 266 pages, $55.00.

ABDOMINAL RADIOLOGY—Editor: James J. McCort, MD; Authors: James J. McCort, MD; Robert E. Mindelzun, MD; Robert G. Filpi, MD, and Charles Rennell, MD. The Williams & Wilkins Company, 428 E. Preston St., Baltimore, MD 21202, 1981. 344 pages, $49.50.

Andrews' DISEASES OF THE SKIN: CLINICAL DERMATOLOGY—Seventh Edition, by Anthony N. Domonkos, MD; Harry L. Arnold, Jr, MD, and Richard B. Odom, MD, W. B. Saunders Company, West Washington Square, Philadelphia, PA 19105, 1982, 1,108 pages, 1,277 illustrations, $58.00 U.S., $69.60, Canada.

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INDICATIONS AND USAGE

RIMSO® - 50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. RIMSO ® - 50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract

CONTRAINDICATIONS

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WARNINGS

Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide This hypersensitivity has been reported in one patient receiving intravesical RIMSO® - 50. The physican should be cognizant of this possibility in prescribing RIMSO® - 50 If anaphylactoid symptoms develop, appropriate therapy should be instituted

PRECAUTIONS

Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count

Intravesical instillation of RIMSO® - 50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation

Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (2.5-12 gm/kg) Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman

Safety and effectiveness in children have not been established

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO® - 50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide

The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration

DOSAGE AND ADMINISTRATION

Instillation of 50 ml of RIMSO® - 50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes Application of an analgesic lubricant gel such as lidocaine jelly to the uretha is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO® - 50 can reduce bladder spasm

In patients with severe interstital cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia. (Saddle block has been suggested)

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(Continued from Page 16)

EMERGENCY MEDICINE

March 15-19—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Islandia Hotel, San Diego. Monday-Friday. 36 hrs. $425.

April 10-17—**Pediatric Emergencies.** UCSD at Kauai, Hawaii. One week. 21 hrs. $325.

April 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, Inc., 2310 Mason St., San Francisco 94133.

May 10-14—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD. Monday-Friday. 36 hrs. $425.

May 21-22—**Modern Concepts in Trauma Care.** Orange County Trauma Society and Mission Community Hospital at Disneyland Hotel, Anaheim. Friday-Saturday. 14 hrs. $195. Contact: John G. West, MD, Orange Co. Trauma Soc., 321 N. Rampart, Suite 120, Orange 92668. (714) 937-5030.

June 7-11—**Postgraduate Institute for Emergency Room Physicians—Symposium III.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs. $425.

June 28-July 2—**Topics in Emergency Medicine.** UCSF. Monday-Friday. 35 hrs. $350.

July 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, Inc., 2310 Mason St., San Francisco 94133.

August 9-13—**Postgraduate Institute for Emergency Room Physicians—Symposium II.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs.

September 13-17—**Postgraduate Institute for Emergency Room Physicians—Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 36 hrs.

September 25-October 1—**American College of Emergency Physicians.** San Francisco. Monday-Thursday. Contact: ACEP, 3900 Capital City Blvd., Lansing, MI 48906.

MEDICINE

March 19-20—**Non-Invasive Cardiology Conference.** Claremont Community Hospital at Sheraton Harbor Island Hotel, San Diego. Friday-Saturday. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

March 20—**The Role of Calcium Channel Blockers in the Treatment of Angina Pectoris.** UCI at Inn at the Park, Anaheim. Saturday. 4 hrs. Contact: Estelle Cohen, Academic Admin., Cardiology Div., UCI Med. Ctr., 101 City Dr. So., Orange 92668. (714) 634-6756.

March 21-24—**Dermatology Consultants' Course.** UCSF at Yosemite. Sunday-Wednesday.

March 26-28—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

March 29-April 2—**Management of Coronary Heart Disease: Medical, Surgical, Exercise.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs.

April-June—**Allergy/Immunology for the Practicing Internist.** UCLA. Wednesday evenings.

April 1-3—**Asthma Update—1982.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Saturday. 19 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 2-7—**Hematology/Oncology Update.** UCD at Ahwahnee Hotel, Yosemite. Friday-Wednesday.

April 3—**Cardiology Update for the Practicing Physician.** American Heart Assn.-Greater Los Angeles Affiliate, San Gabriel Valley Division, at Huntington Sheraton, Pasadena. Saturday. 8 hrs. $55, members; $70, nonmembers. Contact: Gary L. Kossky, AHA, 929 N. Grand Ave., Covina 91724. (213) 339-7382 or (213) 686-2506.

April 14—**Cardiology Update 1982.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

April 14—**23rd Annual Physician's Symposium: Vascular Disease: Cerebral, Cardiac and Peripheral.** American Heart Assn., Santa Clara County Chapter, at LeBaron Hotel, San Jose. Wednesday. 6 hrs. $40, members; $50, nonmembers. Contact: Harriet M. Schutte, RN, PhD, AHA, 3003 Moorpark Ave., San Jose 95128. (408) 247-8555.

April 16—**Injectable Collagen—Applications and Technique.** STAN. Friday. $100. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

April 16-17—**Recent Advances in Renal, Metabolic and Endocrine Disorders.** St. Francis Medical Center at Bonaventure Hotel, Los Angeles. Friday-Saturday. $115. Contact: Allan M. Hoffman, EdD, Dir., Med. Ed., St. Francis Med. Ctr., 3630 E. Imperial Highway, Lynwood 90262. (213) 603-6171.

April 16-18—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

April 22-23—**Infectious Disease Symposium.** Epidemiology Assn. of Greater Sacramento and Mercy Hospital at Red Lion Inn, Sacramento. Thursday-Friday. 14 hrs. Contact: Office of Cont. Med. Ed., Mercy General Hospital, 4001 J St., Sacramento 95819. (916) 453-4545.

April 25-28—**Dermatology.** UCD at Ahwahnee Hotel, Yosemite. One week.

April 28—**Thyroid '82.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Bonnie VanWaardenburg, Coordinator of Symposia, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

May 6-7—**Advances in Infectious Diseases.** UCSF. Thursday-Friday. 14 hrs. $170.

May 7-8—**Common Nervous System Pathology Diagnosis and Treatment.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 14 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 7-9—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

May 15-18—**American Thoracic Society—Annual Scientific Meeting.** Bonaventure Hotel, Los Angeles. Saturday-Tuesday. 30 hrs. $35, members; $100, nonmembers. Contact: S. R. Iannotta, Exec. Dir., ATS, 1740 Broadway, New York 10019. (212) 245-8000.

May 17-21—**Advances in Internal Medicine.** UCSF. Monday-Friday. 40 hrs. $375.

May 21-22—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

May 27-30—**4th Annual Refresher Course in Allergy and Asthma.** UCD at Marriott's Great America, Santa Clara. Thursday-Sunday.

June 7-9—**Clinical Echocardiography—1982: M-Mode, 2-Dimensional and Pulse Doppler Techniques.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Monday-Wednesday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 9—**Bleeding Disorders.** LLU. Wednesday. 4 hrs. $30.

June 11-13—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Aladdin Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

June 25-27—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Newporter Inn, Newport Beach. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

July 10-18—**30th Annual Intensive Review of Internal Medicine.** USC. 9 days

July 16-17—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

July 17-24—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 21 hrs. $325.

August 6-8—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Clouds-Cal Neva Resort, Lake Tahoe. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 13-15—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 20-22—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at Hyatt, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 30-September 4—**Fifth Comprehensive Nephrology Review Course.** UCLA at Marriott, Los Angeles. Monday-Saturday. 28½ hrs. $595.

OBSTETRICS AND GYNECOLOGY

March 20-24—**American Fertility Society.** See Of Interest To All, March 20-24.

March 27-April 3—**Obstetrics and Gynecology.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 2-3—**27th Annual T. Hart Baker, MD, Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at Hotel del Coronado, Coronado. Friday-Saturday. Contact: Lilia M. Guerrero, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

April 19-21—**4th Annual Orange County OB/GYN Congress.** Orange County Ob-Gyn Society and UCI at Newporter Inn, Newport Beach. Monday-Wednesday. 15 hrs. $250. Contact: Secretary, P.O. Box 1297, Orange 92668. (714) 644-1700.

May 10-12—**Recent Advances in OB/GYN.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 20 hrs. $300.

May 19-21—**Perinatal Medicine: Issues and Impact.** Mount Zion Hospital and Medical Center at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday. Contact: Office of Cont. Ed., Mount Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

June 2-5—**Controversies in Obstetrics and Gynecology.** Memorial Hospital Medical Center-UCI Center for Health Education at Silverado Country Club, Napa. Wednesday-Saturday. 20 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

PEDIATRICS

March 17-19—**General Pediatrics.** American Academy of Pediatrics at Royal Lahaina Resort, Maui. Wednesday-Friday. Contact: Dept. of Education, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

March 20-25—**American Academy of Pediatrics—Spring Session.** Sheraton Waikiki, Honolulu. Saturday-Thursday. Contact: Dept. of Education, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

April 3—**Common Endocrine Problems in Adolescence for the Practicing Physician.** Children's Hospital Medical Center of No. Calif. at Marriott Inn, Berkeley. Saturday. 5 hrs. $45. Contact: Eddie Burden, Teen Clinic-Bldg. J, Children's Hosp. Med. Ctr., 51st and Grove Sts., Oakland 94609. (415) 428-3387.

April 10-17—**Pediatric Emergencies.** See Emergency Medicine, April 10-17.

April 14—**Antibiotic Use in Pediatric Specialty Practice.** LLU. Wednesday. 4 hrs. $30.

April 16-17—**Pediatrics: Renal Disease in Children and Adolescents.** UCD at Holiday Inn Holidome, Sacramento. Friday-Saturday. 11 hrs.

April 16-17—**New Directions in Care of the Handicapped Child.** American Academy of Pediatrics and Desert Hospital at Desert Hospital, Palm Springs. Friday-Saturday. 16 hrs. Contact: John Powers, AAP, P.O. Box 1034, Chicago 60602. (800) 323-0797.

April 22-24—**Advances in Pediatrics.** UCSF. Thursday-Saturday. 18 hrs. $250.

April 28-30—**7th Annual Symposium: Care of the Sick Newborn.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 19 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 1—**Pediatric Ophthalmology for the Primary Care Practitioner.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 6 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 3-7—**12th Annual Review of Pediatrics.** USC. Monday-Friday. 32 hrs. $350.

May 19—**Los Angeles Pediatric Society—Annual Spring Meeting.** Hilton, Los Angeles. Wednesday. 2 hrs. $20. Contact: Eve Black, Exec. Sec., P.O Box 2022, Inglewood 90305. (213) 757-1198.

May 29-31—**Challenges in Pediatrics.** Northern California Chapter, American Academy of Pediatrics, at Monterey. Saturday-Monday. Contact: David A. Zlotnick, MD, 3200 Middlefield Rd., Palo Alto 94306.

July 11-12—**First Annual Disneyland Pediatric Seminar.** American Academy of Pediatrics, Calif. Chap. 2, at Disneyland Hotel, Anaheim. Sunday-Monday. 12 hrs. Contact: AAP, Calif. Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

September 29-30—**39th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Hilton, Los Angeles. Wednesday-Thursday. 11 hrs. $145, members; $175, nonmembers. Contact: Eve Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

PSYCHIATRY

March-May—**Mental Research Institute Workshops.** Palo Alto. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

March 27—**Reconsiderations of Psychoanalytic Listening.** Southern California Psychoanalytic Society at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Mrs. Carol Ziff, Exec. Sec., So. Calif. Psychoanalytic Soc., 9024 Olympic Blvd., Beverly Hills 90211. (213) 936-2877.

March 29-April 3—**American Orthopsychiatric Association—**

59th Annual Meeting. Hilton, San Francisco. Monday-Saturday. Contact: AOA, 1775 Broadway, New York 10019. (212) 586-5690.

April 3-4—**Family Therapy by Family Therapists.** Mental Research Institute at Sheraton-Palace, San Francisco. Saturday-Sunday. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

April 23-24—**Psychotherapy and Law Enforcement: Issues and Techniques.** UCSF at Hyatt Regency, San Francisco. Friday-Saturday. Contact: Aveleen Blumenstock, Asst. Dir. of Cont. Ed., Dept. of Psychiatry, UCSF, Langley Porter Institute, Box 2D, 401 Parnassus Ave., San Francisco 94143. (415) 681-8080, ext. 554.

June 3-5—**Depression.** UCD at Del Monte Hyatt, Monterey. Thursday-Saturday.

June 21-25—**Comparative Psychotherapies.** USC at Vacation Village, San Diego. Monday-Friday. 21 hrs. $295.

RADIOLOGY AND PATHOLOGY

March 15-18—**International Workshop on Physics and Engineering in Medical Imaging.** UCI at Asilomar Conference Center, Pacific Grove. Monday-Thursday.

March 15-19—**Diagnostic Radiology.** UCSF. Monday-Friday. 33 hrs. $375.

March 20-21—**B-Scan Ultrasonography: Update.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 8 hrs. $150.

March 24-26—**Gram Negative Organisms: An Approach to Identification.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 20 hrs. Contact: Asst. Dir., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 12-13—**Pathology of Parasitic Infections.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Monday-Tuesday. 17 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 12-15—**Postgraduate Course in Diagnostic Radiology.** Memorial Hospital Medical Center-UCI Center for Health Education at Disneyland Hotel, Anaheim. Monday-Thursday. 24 hrs. Contact: Asst. Dir., UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 30-May 1—**CT of the Lumbar Spine.** UCSF at Fairmont Hotel, San Francisco. Friday-Saturday. 11 hrs. $250.

May 7-8—**Common Nervous System Pathology Diagnosis and Treatment.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 14 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 20-25—**Pathology of the Lung.** UCSD at La Jolla Village Inn, La Jolla. Sunday-Friday. 50 hrs.

July 24-30—**Laboratory Medicine.** USC at Maui Marriott Resort, Maui. One week. 27 hrs. $435.

July 24-August 1—**Diagnostic Radiology: An In-Depth Seminar Approach to Diagnostic Imaging.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. 9 days. 24 hrs. $345.

August 7-14—**Radiology.** USC at Mauna Kea Beach Hotel, Kamuela. One week.

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SURGERY

March 18-19—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

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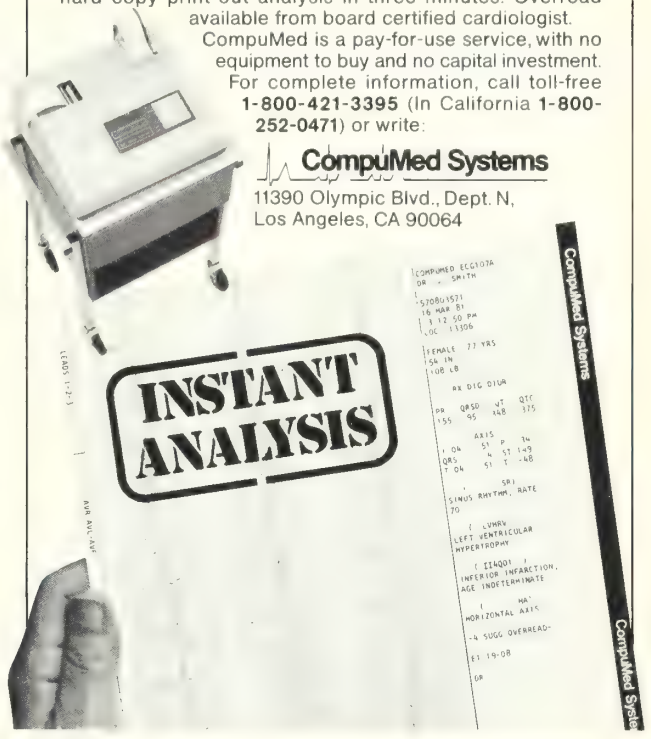

March 25-27—**Diagnosis and Treatment of Retinal, Macular and Vitreous Diseases.** Retina Research Fund of St. Mary's Hospital and Medical Center at Silverado Country Club, Napa. Thursday-Saturday. $225. Contact: Howard Schatz, MD, Retina Research Fund of St. Mary's Hosp., 450 Stanyan St., San Francisco 94117. (415) 921-4860.

March 28-31—**19th Annual Seminar on Controversial Areas in Surgery.** UCLA at Palm Springs. Sunday-Wednesday.

March 29-April 2—**Management of Coronary Heart Disease: Medical, Surgical, Exercise.** See Medicine, March 29-April 2.

March 31-April 4—**10th Annual Symposium on Vascular Surgery.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Sunday. $385.

April 2—**Anterior Vitrectomy—1982.** Sutter Community Hospitals at Sutter General Hospital, Sacramento. Friday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

April 15-17—**Postgraduate Course in General Surgery.** UCSF. Thursday-Saturday.

April 17-24—**Frontiers in Functional Neurosurgery.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 21-23—**American Intra-Ocular Implant Society.** Century Plaza, Los Angeles. Wednesday-Friday. Contact: AIOIS, P.O. Box 3140, Santa Monica 90403. (213) 829-7317.

April 23-24—**Vitrectomy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

April 24-May 1—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $325.

April 25-29—**American Association of Neurological Surgeons.** Honolulu. Sunday-Thursday. 40 hrs. Contact: Selene Patterson, AANS, 625 N. Michigan Ave., Suite 1519, Chicago 60611. (312) 944-4205.

April 26-29—**Southwestern Surgical Congress.** Hotel del Coronado, Coronado. Monday-Thursday. Contact: J. A. Barney, MD, 1211 N. Shartel St., 708 Physicians and Surgeons Bldg., Oklahoma City 73103.

April 30-May 1—**CT of the Lumbar Spine.** See Radiology and Pathology.

May 2-6—**American Society of Colon and Rectal Surgeons—Annual Convention.** San Francisco. Sunday-Thursday. 20 hrs. $125, members: $135, nonmembers. Contact: Harriette Gibson, Admin. Sec., ASCRS, 615 Griswold, Suite 516, Detroit 48226. (313) 961-7880.

May 11-14—**3rd Annual Verne T. Inman/17th Annual LeRoy C. Abbott Lectureship.** UCSF. Tuesday-Friday. 14 hrs. Contact: Eileen Gaines, Alumni Sec., UCSF Dept. of Orthopedic Surgery, U471, San Francisco 94143. (415) 666-1166.

May 12—**Surgical Subspecialties.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Secretary, Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

May 14-15—**Diagnostic Ocular and Orbital Ultrasound Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $125. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

May 21-22—**Modern Concepts in Trauma Care.** Orange County Trauma Society and Mission Community Hospital at Disneyland Hotel, Anaheim. Friday-Saturday. 14 hrs. $195. John G. West, MD, Orange Co. Trauma Soc., 321 N. Rampart, Suite 120, Orange 92668. (714) 937-5030.

June 3-4—**12th Annual Neurosurgery Postgraduate Course.** UCSF at Hilton, San Francisco. Thursday-Friday. 16 hrs. $250.

June 4-7—**Intensive Course in Refractive Keratoplasty: Barraquer Technique.** Jules Stein Eye Institute, Los Angeles. Friday-Monday. 32 hrs. $1,750. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

June 19-26—**Medical and Surgical Management of Ocular Inflammation.** USC at Mauna Kea Beach Hotel, Kamuela. One week. 26½ hrs. $435.

August 12-14—**Selection and Technique for Use of Muscle and Musculocutaneous Flaps in Reconstructive Surgery.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 20 hrs. $420.

August 14-25—**Update: Surgery 1982.** USC at Sheraton Waikiki, Honolulu, and Maui Marriott Resort, Maui. 12 days. 35 hrs. $425.

September 1-3—**International Cochlear Symposium.** UCSF at Holiday Inn Union Square, San Francisco. Wednesday-Friday.

OF INTEREST TO ALL PHYSICIANS

March 15-19—**Sports Medicine.** Univ. of Hawaii at Princess Kaiulani Hotel, Waikiki, Honolulu. Monday-Friday. 18 hrs. $250. Contact: Joy Lewis, Box CE-CCECS, 2530 Dole St., Honolulu 96822. (808) 948-8244.

March 18-21—**Clinical Management.** STAN at The Lodge, Pebble Beach. Thursday-Sunday. 12 hrs. $175.

March 19—**Diabetes and Nutrition Update.** UC and STAN at Hilton, San Francisco. Friday. Contact: UCD.

March 19-21—**In Pursuit of Wellness.** UCSF at Jack Tar Hotel, San Francisco. Friday-Sunday. $75. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

March 20—**Sleep Disorders: Diagnosis and Treatment.** UCLA. Saturday. 7 hrs. $90.

March 20-24—**American Fertility Society—38th Annual Meeting and 15th Postgraduate Program.** MGM Grand, Las Vegas. Saturday-Wednesday. Contact: Herbert H. Thomas, MD, Med. Dir., AFS, 1608 13th Ave. S., Suite 101, Birmingham, AL 35256. (205) 933-7222.

March 20-27—**Medical Genetics for Health Professionals.** San Jose State University. One week. 15 hrs. Contact: Kate Wright-Rodgers, MPH, Cont. Ed., San Jose State Univ., Washington Square, San Jose 95192. (408) 277-3778.

March 25-26—**Common Problems in Office Practice.** LLU at Casa Royale Motor Inn, Bakersfield. Thursday-Friday. 6 hrs.

March 25-27—**Third Annual Dermatology Conference: Dermatology for Non-Dermatologists.** Eisenhower Medical Center and Stanford at Annenberg Center for Health Sciences, Eisenhower Med. Ctr., Rancho Mirage. Thursday-Saturday. Contact: P. Kokemueller, MS, Conf. Services Mgr., Annenberg Ctr. for Health Sciences, Eisenhower Med. Ctr., 39000 Bob Hope Dr., Rancho Mirage 92270.

March 27-April 3—**Otolaryngology for Non-Otolaryngologists.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 3-10—**Topics in Family Practice.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 10-17—**Management of Pain.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 17—**Nutritional Concerns in the Hospitalized Patient.** Fresno Community Hospital and Medical Center at Hilton, Fresno. Saturday. 8 hrs. $50. Contact: Education and Training Dept., Fresno Community Hosp. and Med Ctr., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

April 22-24—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 22-25—**Wound Management.** UCSD at Hilton, San Diego. Thursday-Sunday. 20 hrs.

April 22-25—**Mountain Medicine.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Friday-Sunday. 19 hrs.

April 30-May 1—**Acute Medical Care—1982—8th Annual Spring Meeting.** Providence Hospital at Marriott Inn, Berkeley. Friday-Saturday. $25. Contact: Medical Staff Office, Providence Hosp., Box 23020, Oakland 94623. (415) 874-8003.

May 1-8—**Diagnostic and Therapeutic Skills.** USC at Hawaii. One week. 29 hrs. $425.

May 2-5—**Medical Evaluation of the Preoperative Patient.** UCD at Del Monte Hyatt, Monterey. Sunday-Wednesday. 17 hrs. $245.

May 2-5—**American Medical Informatics Association Congress 82—First Annual Joint Conference.** AMIA, Soc. for Advanced Medical Systems, Soc. for Computer Medicine, Internat'l Health Evaluation Assn., Salutis Unitas, Univ. of Missouri-Columbia Health Care Technology Ctr., IL Conf. on Medical Information Systems, at Hyatt on Union Square, San Francisco. Sunday-Wednesday. Contact: M. F. Collen, MD, 3451 Piedmont Ave., Oakland 94611.

May 3-7—**Symposium on Non-Emergent Outpatient Care.** UCSD at Hilton, San Diego. Monday-Friday. 27 hrs. $325.

May 3-9—**Basic Diving Medicine.** UCSF at Fresno. One week. Contact: Vincent S. O'Hara, MD, VA Medical Center, 2615 E. Clinton, Fresno 93703. (209) 225-6100, ext. 345.

May 6-9—**Association of Clinical Scientists.** Miramar Sheraton, Los Angeles. Thursday-Sunday. Contact: F. W. Sunderman, Jr., MD, Dept. of Laboratory Medicine, Univ. of Connecticut Sch. of Med., 263 Farmington Ave., Farmington, CT 06032.

May 9-13—**Association for the Advancement of Medical Instrumentation.** Hyatt Regency, San Francisco. Monday-Thursday. Contact: M. J. Miller, Exec. Dir., Assn. for the Advancement of Medical Instrumentation, 1901 N. Ft. Myer Dr., Suite 602, Arlington, VA 22209.

May 9-14—**Fingers-to-Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Friday. 40 hrs. $375.

May 12—**Common Fractures.** LLU. Wednesday. 4 hrs. $30.

May 22-23—**Conference on Health Problems Related to the Chinese in America.** Chinese Hospital and UCSF at Holiday Inn/Financial District, San Francisco. Saturday-Sunday. 12 hrs. $85. Contact: Elizabeth S. Weston, Chinese Hosp., 845 Jackson St., San Francisco 94133. (415) 982-2400, ext. 215.

May 31-—June 4—**9th Annual Joint UCLA-Santa Monica Hospital Medical Center Family Practice Refresher Course.** Miramar-Sheraton, Santa Monica. Monday-Friday. 35 hrs. Contact: UCLA.

June 9-11—**7th Annual Conference: Clinical Application of Hyperbaric Oxygen.** Memorial Hospital Medical Center at Disneyland Hotel, Anaheim. Wednesday-Friday. 24 hrs. Contact: Baromedical Dept., Memorial Hosp. Med Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3613.

June 14-19—**UCI Family Practice Refresher Course.** Marriott, Newport Beach. Sunday-Friday. 50-56 hrs.

July 6-8—**Family Practice Board Review Course.** UCSF. Tuesday-Thursday.

July 9-11—**Sensory Systems' Influence on Movement and Tone —10th Annual Sensorimotor Integration Symposium.** UCSD at Holiday Inn at the Embarcadero, San Diego. Friday-Sunday.

August 12-13—**National Institute for Care of the Elderly.** Univ. of Nevada-Reno School of Medicine at MGM Grand, Reno. Thursday-Friday. 12 hrs. Contact: Leanne Stone, Cont. Ed., Univ. of Nevada-Reno, Reno 89557. (702) 784-4046.

August 13-14—**6th Annual Sports Medicine Conference.** Univ. of Nevada-Reno School of Medicine at MGM Grand, Reno. Friday-Saturday. 12 hrs. Contact: Leanne Stone, Cont. Ed., Univ. of Nevada-Reno, Reno 89557. (702) 784-4046.

August 14-25—**25th Annual Postgraduate Refresher Course.** USC at Sheraton Waikiki, Honolulu, and Maui Marriott Resort, Maui. 12 days. 37 hrs. $425.

August 16-20—**Advanced Diving Medicine.** UCSF at San Diego. Monday-Friday.

August 23-September 3—**Intensive Residency in Occupational Medicine, Session. I.** UCSF at Golden Gateway Holiday Inn, San Francisco. 12 days. 80 hrs. $1,000.

September 4-7—**American Academy of Family Physicians.** San Francisco. Saturday-Tuesday. Contact: Roger Tusken, Exec. Dir., AAFP, 1740 W. 92nd St., Kansas City, MO 64114.

September 16-18—**Postgraduate Institute on Geriatrics.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA

See Washington Listings: March 18-19, 24; May 3, 4, 6-7, 26; June 7, 8, 17-18.

IDAHO

See Washington Listings: March 15, April 19, May 29 and June 14.

MONTANA

March 20-March 27—**Pulmonary Diseases: A Practical Approach.** Big Sky. Saturday-Saturday. 20 Category I credit hours; also 20 AAFP Elective hours, and 20 ACEP hours. Fee: $260 for Physicians; $180 for Physicians Assistants, Interns and Residents. Contact: M. S. M. Watts, MD, Associate Dean and Director, University of California, San Francisco, Extended Programs in Medical Education, San Francisco, CA 94143. Telephone—For Registration: (415) 666-2894 or 666-2483; for Program Information: (415) 666-4251.

See Washington Listings: March 24, 25, 26; April 15-17, 21, 22, 23; May 26, 27, 28; June 7 and 8.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

March 13—**Infectious Disease Update Seminar.** Albuquerque. Saturday. Four Seasons Motor Inn. 7½ credit hours, also AAFP Prescribed. Contact: Martin J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd. SE, Albuquerque, NM. (505) 842-7000.

March 16-21—**Purgatory Medical Ski Symposium.** Durango, Colorado. Tuesday-Sunday. Iron Horse Resort & Convention Center. 24 credit hours, also AAFP Prescribed. Contact: David R. Holten, MD, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

March 18-19—**Advanced Trauma Life Support Provider's Course.** Albuquerque. Thursday-Friday. UNM Family Practice Building. 16 hours credit, also AAFP Prescribed. Contact: William Schiller, MD, Director, Burn & Trauma Unit, UNM Hospital, Albuquerque, NM 87131. (505) 843-2231.

March 19—**Recent Advances in Cerebrovascular Disease and New Neuroradiologic Techniques.** Albuquerque. Lovelace Medical Center. 4 credit hours. Contact: Martin J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd. SE, Albuquerque, NM 87108. (505) 842-7000.

March 19-20—**Arthritis in Childhood.** Albuquerque. Friday-Saturday. AMFAC Hotel. 10 credit hours, also AAFP Pre-

scribed. Contact: The Arthritis Foundation, New Mexico Chapter, PO Box 8022, Albuquerque, NM 87108. (505) 265-1545.

March 30-31—**Base Station Physician Course.** Taos. Tuesday-Wednesday. Sagebrush Inn. 9 credit hours, also AAFP Prescribed. Contact: Arleen L. Sadowsky, MD, President, NM Chapter American College of Emergency Physicians, 6320 Palma Pl. NW, Albuquerque, NM 87120.

April 1-3—**New Mexico Chapter, American College of Emergency Physicians Meeting.** Taos. Thursday-Saturday. Sagebrush Inn. 18 credit hours, also AAFP Prescribed. Contact: Arleen L. Sadowsky, MD, President, 6320 Palma Pl. NW, Albuquerque, NM 87120.

April 23-24—**Geriatrics Medicine Update—1982.** Albuquerque. Friday-Saturday. AMFAC Hotel. 10 credit hours, also AAFP Prescribed. Contact: UNM School of Medicine, Office of CME, Albuquerque, NM 87131. (505) 277-3942.

May 5-7—**New Mexico Medical Society Annual Meeting.** Santa Fe. Wednesday-Friday. Hilton Inn. 10 credit hours, also AAFP. Contact: NMMS, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

May 14-15—**15th Annual OB/GYN Update.** Albuquerque. Friday-Saturday. AMFAC Hotel. 10 credit hours, also AAFP Prescribed. Contact: UNM School of Medicine, Office of CME, Albuquerque, NM 87131. (505) 277-3942.

June 4-5—**Recent Advances in the Diagnosis and Treatment of Coronary Artery Disease.** Albuquerque. Friday-Saturday. Veterans Administration Medical Center. 10 credit hours, also AAFP Prescribed. Contact: American Heart Association, 2403 San Mateo Blvd., Albuquerque, NM 87108. (505) 884-3717.

June 17-19—**Radiology for Primary Care Physicians 1982—An Update.** Santa Fe. Thursday-Saturday. Symposia de Santa Fe. 15 credit hours, also AAFP Prescribed. Contact: Marcus J. Smith, MD, PO Box 5175, Santa Fe, NM 87501. (505) 982-5218.

July 8-10—**25th Annual Meeting, New Mexico Ophthalmological Society.** Santa Fe. Thursday-Saturday. Hilton Inn. 8 credit hours. Contact: Walter J. Levy, MD, 465 St. Michael's Dr., Santa Fe, NM 87501. (505) 982-1911.

July 19-22—**25th Annual Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 credit hours. Also AAFP Prescribed. Contact: Convention Director, NM Academy of Family Physicians, PO Box 456, Sunland Park, NM 88063. (505) 247-0539 or (915) 533-3449.

July 23-25—**11th Annual Santa Fe Cardiology Symposium.** Santa Fe. Friday-Sunday. Inn at Loretto. 14 credit hours, also AAFP Prescribed. Contact: Meeting Director, Southwest Cardiology Associates, 8100 Constitution NE, Albuquerque, NM 87110. (505) 292-1114.

October 7-9—**The Clinical Spectrum of Adult Heart Disease.** Albuquerque. Thursday-Saturday. University of New Mexico School of Medicine Auditorium. Hour for hour credit, also AAFP Prescribed. Contact: Jonathan Abrams, MD, UNM, School of Medicine, Dept. of Cardiology, Albuquerque, NM 87131. (505) 277-4253.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the Ameri-

can Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

'EDIATRIC GRAND ROUNDS

'rimary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

NTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

MKSAP V REVIEW

Sponsors: Utah Region, American College of Physicians/Utah Society of International Medicine/University of Utah) Jniversity Medical Center, Salt Lake City

)ctober 1981-June 1982 (Ongoing)—Thursdays. 2 hrs. Fee for Optional Materials: $160 (ACP non-members); $60 (ACP members). Contact: John Holbrook, MD (801) 581-7818.

* * * *

March 13-20—**First Annual Oculo-Plastic SRI Meeting** (Sponsor: University of Utah). Park City. Saturday-Saturday. 15 hrs. Fee: $225. Contact: Darrel Wolfley, MD (801) 363-3355.

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

March 15-19—**Second Annual Nutrition in Contemporary Medicine Course** (Sponsor: University of Utah). Park City. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 18-19—**Infection Control Update—Rocky Mountain Infection Control Association (RMICA)** (Sponsor: University of Utah). Salt Lake City. Thursday-Friday. Little America. 12 hrs. Fee: $75. Contact: Sego Matsumiya (801) 582-1565.

March 19—**Continuous Ambulatory Peritoneal Dialysis** (Sponsor: University of Utah, Department of Artificial Organs). Salt Lake City. Friday. University of Utah Campus. Credit: To be announced. Fee: $30. Contact: Claire Turner (801) 581-5809.

March 21-28—**Park City Dermatological Seminar** (Sponsors: St. Mark's Hospital, University of Utah, Intermountain Dermatology Foundation [IDF]). Park City. Sunday-Sunday. Shadow Ridge Condo Hotel. 20 hrs. Fee: $250. Contact: IDF, 1151 East 3900 South, Salt Lake City 84117 (801) 268-0435.

March 24-25—**Genetics: Impact of Genetic Disorders on the Family** (Sponsor: University of Utah). Salt Lake City. Wednesday-Thursday. University of Utah Medical Center. 12 hrs. Fee: $50-$65. Contact: John Carey, MD, (801) 581-8943.

March 26-27—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

March 27-28—**The Complexities of Interpreting CT Scans in Cervical and Lumbar Disc Disease** (Sponsors: Western Neurological Associates/St. Mark's Hospital). Salt Lake City. Marriott Hotel. Monday-Tuesday. 10 hrs. Fee: $225. Contact: Linda June Krueger (801) 262-3441.

April 7-9—**Health Hazards of Minerals and Mining: 4th Annual Park City Environmental Health Conference** (Sponsors: University of Utah/Rocky Mountain Center for Occupational and Environmental Health). Park City. Monday-Wednesday. 24 hrs. Fee: $300. Contact: Katharine Blosch (801) 581-5710.

April 15-17—**First Annual Clinical Ophthalmology Meeting at Snowbird** (Sponsor: University of Utah). Snowbird. Tuesday-Thursday. 9 hrs. Fee: $50. Contact: Rebecca Olsen (801) 581-6384.

May 14-15—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

June 11-12—**Medical Aspects of Laser Surgery** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Little America. Credit and fee to be announced. Contact: John Dixon, MD (801) 581-8201.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

March 15—**(IDAHO) Site Visit.** Boise. Monday. Contact: U/W.

March 16—**Prevention/Treatment Thromboembolism.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

March 16—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

March 17—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

March 17—**Vasculitis.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

March 18-19—**(ALASKA) Stress Management With Children.** Anchorage. Thursday-Friday. Contact: U/W.

March 19—**Common Psychiatry Problems for Primary Care.** Seattle. Friday. Glacier Auditorium, Swedish Hospital. Contact: U/W.

March 19-20—**The Office Management of Common Psychiatric Problems.** Seattle. Friday-Saturday. U/W Health Sciences Bldg. Contact: U/W.

March 19-20—**Days of Pediatrics.** Tacoma. Friday-Saturday. Contact: CME Pierce County.

March 22—**Diagnosis and Management of Vasculitis.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

March 24—**(MONTANA) Recent Advances in Hematology.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

March 24—**(ALASKA) Cancer & Pregnancy.** Anchorage. Wednesday. Contact: U/W.

March 24-27—**(BRITISH COLUMBIA, CANADA) North Pacific Society of Neurology and Psychiatry.** Victoria, BC. Wednesday-Saturday. Empress Hotel. Contact: I. Blake Thompson, MD, 407-1120 Yates Street, Victoria, BC V8V-3M9, Canada.

March 25—**(MONTANA) Recent Advances in Hematology.** Billings. Marillac Hall. Contact: U/W.

March 26—**(MONTANA) Recent Advances in Hematology.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

March 26-27—**Recombinant DNA and the Clinician.** Seattle. Friday-Saturday. U/W South Campus Center. Contact: U/W.

March 27-April 3—**(HAWAII) Obstetrics and Gynecology.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 27-April 3—**(HAWAII) Otolaryngology for Non-Otolaryngologists.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

March 29-April 9—**Rehabilitation Medicine Review.** Bellevue. Monday-Friday. Bellevue Hilton. Contact: U/W.

March 31, April 7, 14, 21, 28, May 5—**Medicine and Civilization.** Seattle. Wednesdays. U/W Health Sciences Building. Contact: U/W.

April 1-3—**Advanced Cardiac Life Support.** Tacoma. Thursday-Saturday. Allenmore Medical Center. Contact: D. Terry Kendrick, MD, Pierce County College of Medical Education, 705 South Ninth, #203, Tacoma, WA 98405. (206) 627-7137.

April 3-10—**(HAWAII) Topics in Family Practice.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 8—**Dermatology Conference.** Everett. Thursday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

April 9-10—**Management of Obesity: Scientific Approach.** Seattle. Friday-Saturday. Park Hilton. Contact: U/W.

April 10—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

April 10-17—**(HAWAII) Management of Pain.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 14—**Alcoholism.** Tacoma. Wednesday. Puget Sound Hospital. Contact: CME Pierce County.

April 15-17—**Eleventh Annual Refresher Course in Diagnostic Radiology and Spinal CT Symposium.** Spokane. Thursday-Saturday. Sacred Heart Medical Center. Contact: Marvin J. Gottschall, MD, Director of Radiology, Sacred Heart Medical Center, TAF-C9, Spokane, WA 99220. (509) 455-3131.

April 15-17—**(MONTANA) Cytology Continuing Education Workshop.** Billings. Thursday-Saturday. Contact: CME Harborview.

April 17-24—**(HAWAII) Frontiers in Functional Neurosurgery.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 19—**(IDAHO) Early Cervical Cancer.** Boise. Monday. Contact: U/W.

April 20—**Detection/Rx Early Cervical Cancer.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

April 21—**Interstitial Lung Disease.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

April 21—**(MONTANA) What's New in Diabetes.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

April 22—**(MONTANA) What's New in Diabetes.** Billings. Thursday. Marillac Hall. Contact: U/W.

April 22-23—**Vascular Disease 1982: A Comprehensive Review for Primary Physicians.** Seattle. Thursday-Friday. South Campus Center. Contact: U/W.

April 23—**Surgical Club Annual Meeting.** Tacoma. Friday. Tacoma General Hospital. Contact: CME Pierce County.

April 23—**(MONTANA) What's New in Diabetes.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

April 26—**Urinary Infections New Developments in Nosocomial Infections.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

April 28—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

April 28-30—**Children's Orthopedic Hospital and Medical Center 75th Anniversary Pediatric Symposium.** Seattle. Wednesday-Friday. Children's Orthopedic Hospital and Medical Center. Contact: Donna Neumann, Medical Administration Office, Children's Orthopedic Hospital and Medical Center, P.O. Box 65371, Seattle, WA 98105. (206) 634-5377.

April 29-May 1—**Trauma.** Seattle. Thursday-Saturday. South Campus Center. Contact: U/W.

May 3—**Site Visit.** Omak. Monday. Contact: U/W.

May 3—**(ALASKA) Site Visit.** Ketchikan. Monday. Contact: U/W.

May 4—**(ALASKA) Site Visit.** Anchorage. Tuesday. Contact: U/W.

May 4—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

May 6-7—**(ALASKA) Cross Cultural Child Psychiatry.** Anchorage. Thursday-Friday. Contact: U/W.

May 7—**The Foot.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

May 13-15—**Third Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 14—**Medical Alumni.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

May 14-15—**Therapeutics in Common Medical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 19—**Breast Cancer & Acute Leukemia.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

May 20—**Estrogen Controversy.** Tacoma. Thursday. Contact: CME Pierce County.

May 20-22—**3rd Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 24—**Fever Unknown Origin/Dx Elderly Dementia.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

May 26—**(ALASKA) Vaginitis.** Anchorage. Wednesday. Contact: U/W.

May 26—**(MONTANA) Health Problems of Physicians.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

May 27—**(MONTANA) Health Problems of Physicians.** Billings. Thursday. Marillac Hall. Contact: U/W.

May 26—**(MONTANA) Site Visit.** Kalispell. Wednesday. Contact: U/W.

May 27—**(MONTANA) Site Visit.** Whitefish. Thursday. Contact: U/W.

May 27-28—**Current Concepts in Management of Joint Disease.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

May 28—**(MONTANA) Health Problems of Physicians.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

May 29—**(IDAHO) Site Visit.** Pocatello. Saturday. Contact: U/W.

June 3-5—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

June 7—**(MONTANA) Site Visit.** Kalispell. Monday. Contact: U/W.

June 7—**(ALASKA) Site Visit.** Ketchikan. Monday. Contact: U/W.

June 8—**(ALASKA) Site Visit.** Anchorage. Tuesday. Contact: U/W.

June 8—**(MONTANA) Site Visit.** Whitefish. Tuesday. Contact: U/W.

June 10-12—**Common Minor Surgeries.** Seattle. Thursday-Saturday. Park Hilton. Contact: U/W.

June 14—**(IDAHO) Vaginitis.** Boise. Monday. Contact: U/W.

June 14—**Site Visit.** Omak. Monday. Contact: U/W.

June 15—**Vaginitis.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

June 15—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

June 16—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

June 17-18—**(ALASKA) Behavior Medicine for GP's.** Anchorage. Thursday-Friday. Contact: U/W.

June 19-23—**(BRITISH COLUMBIA, CANADA) Canadian Congress of Laboratory Medicine & Pacific Northwest Society of Pathologists Meeting.** Vancouver, BC. Saturday-Wednesday. Hotel Vancouver. Contact: G. R. Gray, MD, 201-660 West Seventh Avenue, Vancouver, BC V5Z IB5.

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WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: June 6-8, 1982, Chena Hot Springs.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. House of Delegates' Annual Meeting: May 28-29, 1982, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 12-17, 1982, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 21-24, 1982, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 11-14, 1982, Hilton Hawaiian Village, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 28-31, 1982, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 30-November 2, 1982, Sheraton, Great Falls.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 14-16, 1982, MGM Grand Hotel, Reno.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. Annual Meeting: May 5-7, 1982, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: November 3-5, 1982, Thunderbird, Jantzen Beach.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: September 14-17, 1982, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 7-10, 1982, Towne Motel, Yakima.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 30-July 3, 1982, Jackson Lake Lodge, Moran.

June 21-25—**Internal Medicine Review.** Seattle. Monday-Friday. Park Hilton. Contact: U/W.

June 23-27—**(OREGON) Modern Medical Practice.** Ashland. Wednesday-Sunday. Ashland Inn. Contact: U/W.

June 24-25—**EKG Interpretation and Arrythmias.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

June 24-26—**Scientific Aspects of Dance.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact: U/W.

June 28—**Recent Advances in Hematology.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

July 15-16—**Surviving the Elements.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

July 23-25—**Washington State Society of Anesthesiologists: Seafair IV Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center. Contact: VMMC.

July 30-31—**Infertility.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

August 19-21—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

September 8-15—**13th International Cancer Congress.** Seattle. Wednesday-Wednesday. Seattle Center. Contact: Congress Operations Office, 13th International Cancer Congress, Fourth and Blanchard Building, Suite 1800, Seattle, WA 98121. (206) 621-9440.

September 16-18—**(WYOMING) Cytology Continuing Education Workshop.** Jackson. Thursday-Saturday. Contact: CME Harborview.

September 23-25—**Cytology Continuing Education Workshop.** Renton. Thursday-Saturday. Valley General Hospital. Contact: CME Harborview.

WYOMING

June 30-July 3—**Wyoming Medical Society Annual Meeting.** Moran. Wednesday-Saturday. Jackson Lake Lodge. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne. WY 82001. (307) 635-2424.

See Washington listing, September 16-18, 1982.

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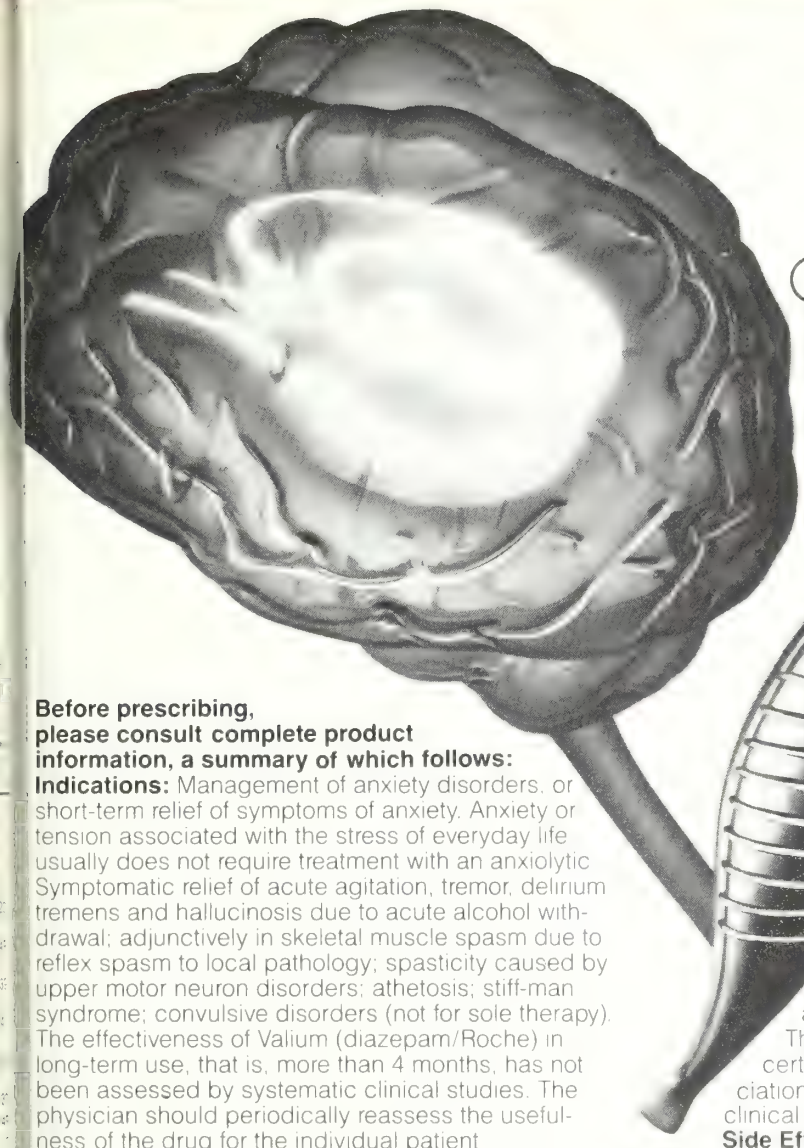


Only Valium® (diazepam/Roche) is indicated in anxiety disorders and as an adjunct in the relief of skeletal muscle spasm

Before prescribing, please consult complete product information, a summary of which follows:
Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy). The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient
Contraindicated: Known hypersensitivity to the drug Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy
Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation

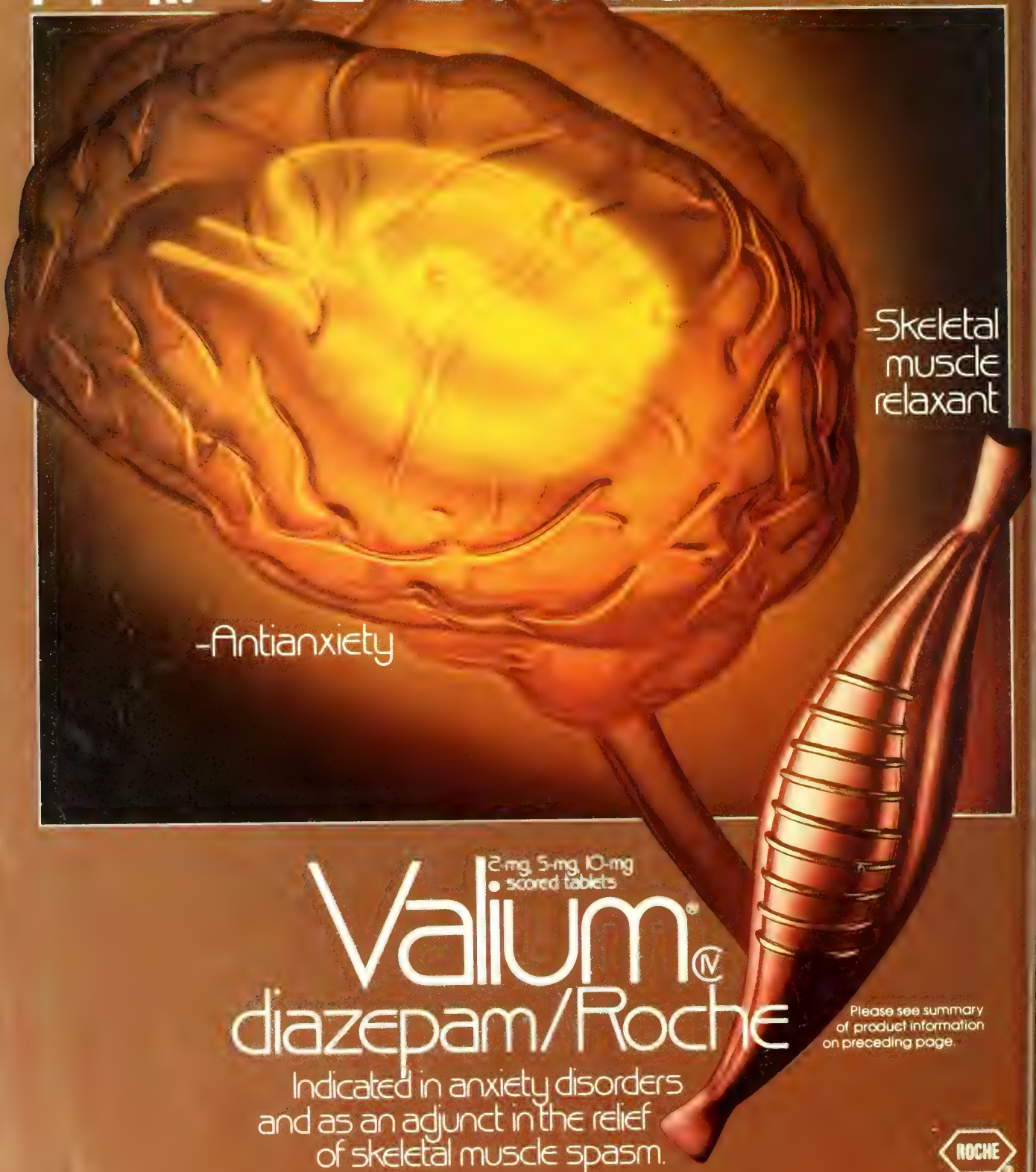
The clearance of Valium (diazepam/Roche) and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice; skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy
Dosage: Individualize for maximum beneficial effect *Adults.* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).
How Supplied: For oral administration, Valium scored tablets—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100* and 500;* Prescription Paks of 50, available in trays of 10.* Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25,† and in boxes containing 10 strips of 10.†

* Supplied by Roche Products Inc., Manati, Puerto Rico 00701
† Supplied by Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, New Jersey 07110

ROCHE
ROCHE PRODUCTS INC
Manati, Puerto Rico 00701

Only Valium® (diazepam/Roche)
has these two distinct effects

mind & muscle



2-mg, 5-mg, 10-mg scored tablets

Valium® (IV) diazepam/Roche

Please see summary of product information on preceding page.

Indicated in anxiety disorders and as an adjunct in the relief of skeletal muscle spasm.

ROCHE

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★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association**

11092-021 820319RELMAN**AS01*
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THE NEW ENGLAND JOURNAL *
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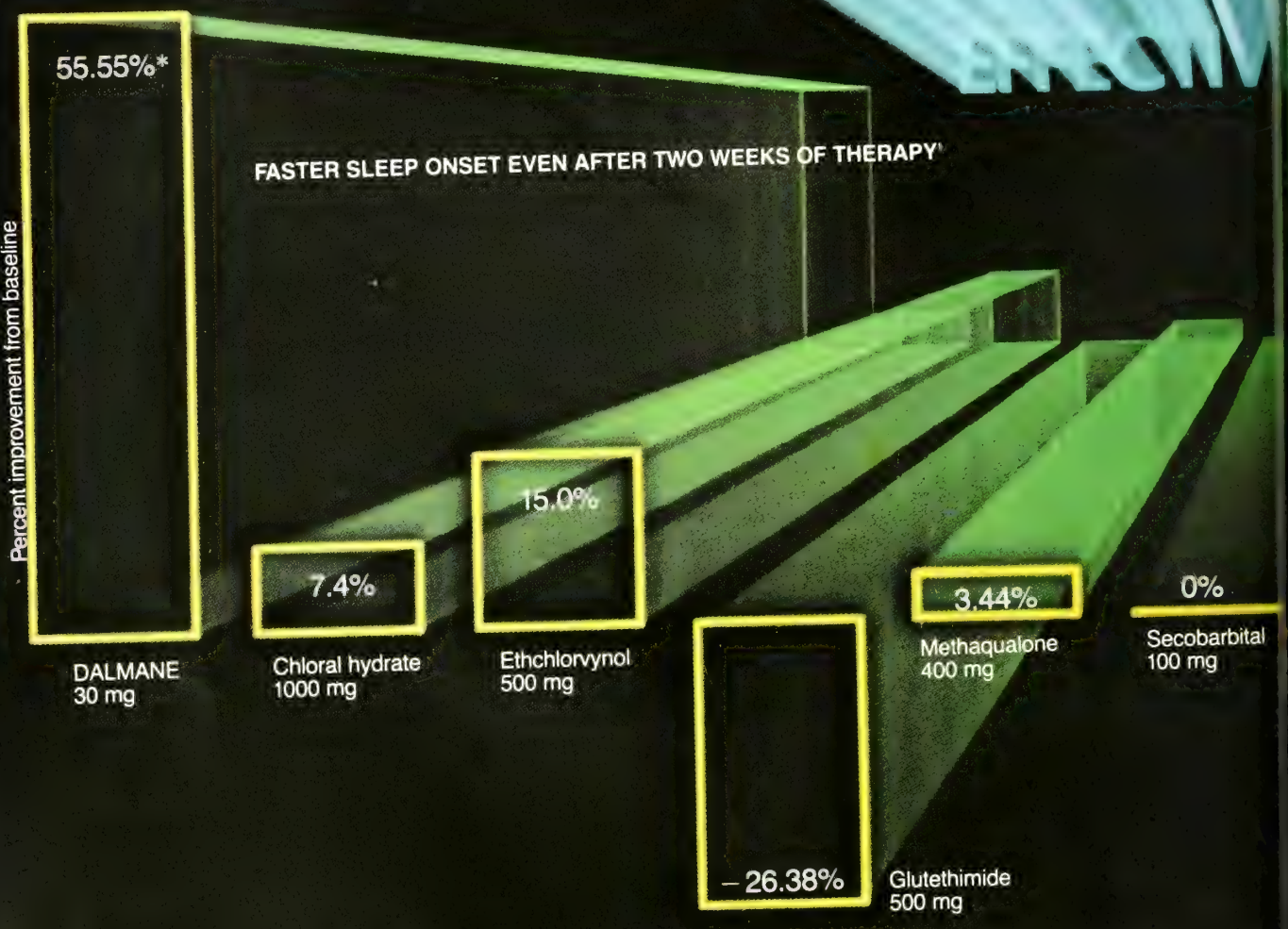
EFFECTIVE



THE MOST INTENSIVELY STUDIED SLEEP MEDICATION

Efficacy of Dalmane (flurazepam HCl/Roche) has been documented in 9141 insomniac patients evaluated in 185 clinical studies. In addition, Dalmane efficacy has been proven in the sleep research laboratory during 995 subject nights.[2]

WITH AN UNSURPASSED RECORD OF SAFETY

In a study of 2542 hospitalized medical patients with insomnia, adverse reactions were reported in only 3.1% or 78 patients. These reactions consisted predominantly of unwanted residual drowsiness; none were considered serious by attending physicians.[3] Safety has also been demonstrated by lack of interference with many commonly ordered laboratory tests [4,5] and no unacceptable fluctuation in prothrombin time in patients on chronic warfarin therapy.[6,7]

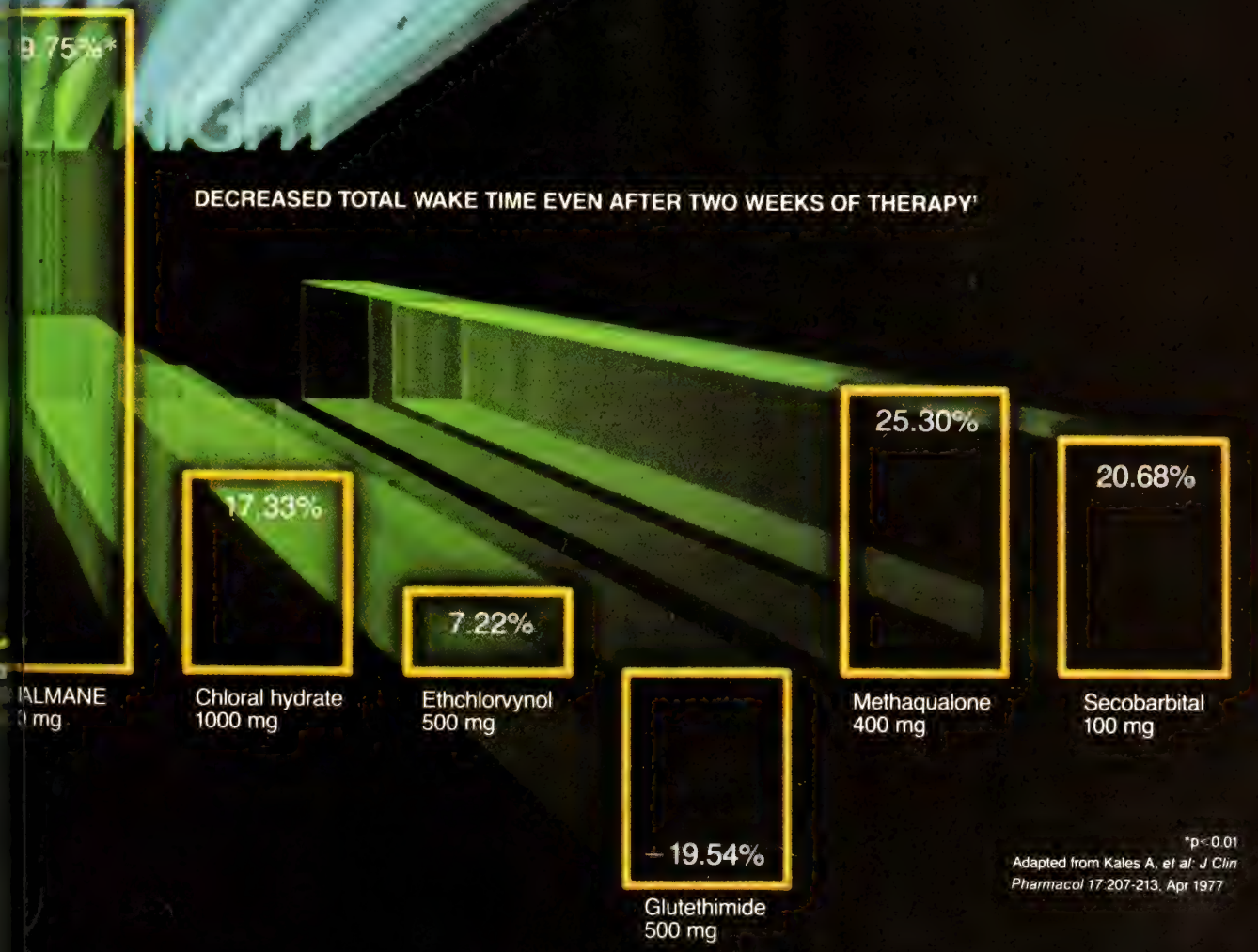
AND SLEEP WITHIN 17 MINU NO WORSENING OF SLEEP ON DISCONTINUATI

Rapid sleep induction, within 17 minutes on average,[3] sets the s for insomnia relief, with improve ment that continues.

In reviewing the experience a discontinuation of Dalmane (flurazepam HCl/Roche) for pe ranging up to 14 nights, no wors ing of sleep compared with bas was observed.[8]

Should insomnia recur, the pa may require guidance in setting regular sleep program to help p

ALL NIGHT



he optimum environment for
nset of natural sleep. If hypnot-
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g in hazardous occupations
ing complete mental alertness
as operating machinery or
a motor vehicle after ingesting
ug.

DALMANE® C IV
flurazepam HCl/Roche

THE STANDARD OF HYPNOTIC EFFICACY FROM THE LEADER IN SLEEP RESEARCH

ROCHE®

Please see following page for a summary of product information.

SLEEP-SPECIFIC DALMANE® (IV)

flurazepam HCl/Roche

One 15-mg capsule *h.s.*–recommended initial dosage for elderly or debilitated patients.
One 30-mg capsule *h.s.*–usual adult dosage
(15 mg may suffice in some patients)

THE STANDARD FOR HYPNOTIC EFFICACY WITH IMPORTANT ADDED BENEFITS

- Well tolerated[2]
- No chemical interference with many commonly ordered laboratory tests, including triglycerides, uric acid, glucose, SGOT, alkaline phosphatase and total protein[4,5] (See adverse reactions section of complete product information.)
- Compatible with chronic warfarin therapy; no unacceptable fluctuation in prothrombin time reported[6,7]

UNLIKE NONSPECIFIC MEDICATIONS USED FOR SLEEP

Tricyclic antidepressants

–which are *not* sleep specific,[9] yet are sometimes used in nondepressed patients for sleep

–which can cause transient insomnia in the elderly[10]

–which can require careful monitoring in cardiovascular patients[10]

–which have strong anticholinergic effects[10]

Antihistamines

–which are *not* reliable sleep-inducing agents[11]

–which may produce stimulation instead[11]

–which have anticholinergic effects[11]

Major tranquilizers

–whose side effects may be troublesome for nonpsychotic patients[12]

–where tolerance for sedation appears rapidly[12]

Dalmane does not cause significant worsening of sleep beyond baseline levels upon discontinuation.[8]

References: **1.** Kales A, *et al: J Clin Pharmacol* 17:207-213, Apr 1977 **2.** Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **3.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther* 21:355-361, Mar 1977 **4.** Moore JD, Weissman L: *J Clin Pharmacol* 16:241-244, May-Jun 1976 **5.** Spiegel HE: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **6.** Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, pp. 641-646 **7.** Warfarin Study: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **8.** Kales A, *et al: Clin Pharmacol Ther* 18:356-363, Sep 1975 **9.** Baldessarini RJ: Drugs and the treatment of psychiatric disorders, chap. 19, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co. Inc., 1980, pp. 391-447 **10.** Cole JO, Davis JM: Antidepressant drugs, chap. 31.2, in *Comprehensive Textbook of Psychiatry/II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2. Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp. 1941-1956 **11.** Douglas WW: Histamine and 5-hydroxytryptamine (serotonin) and their antagonists, chap. 26, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co. Inc., 1980, pp. 609-646 **12.** Davis JM, Cole JO: Antipsychotic drugs, chap. 31.1, in *Comprehensive Textbook of Psychiatry/II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2. Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp. 1921-1940

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.

Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

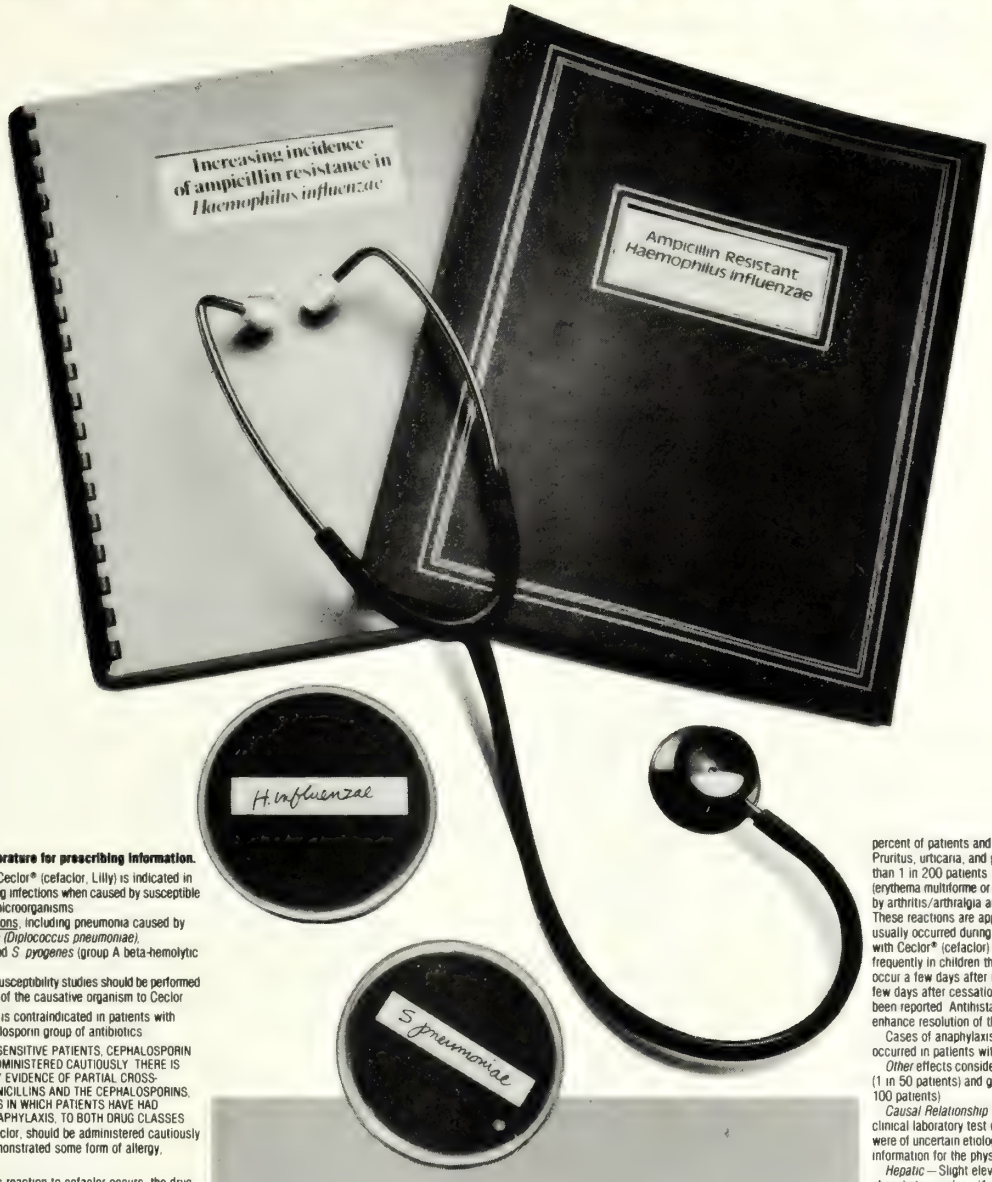
Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients*: 15 mg recommended initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

ROCHE®

ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

An added complication... in the treatment of bacterial bronchitis*


Increasing incidence of ampicillin resistance in Haemophilus influenzae
Ampicillin Resistant Haemophilus influenzae
H. influenzae
S. pneumoniae

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coomb testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90)

As with other broad-spectrum antibiotics, colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with Ceclor

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor® (cefaclor). Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [100281R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[8]

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information

References

1. Antimicrob. Agents Chemother., *8*:91, 1975
2. Antimicrob. Agents Chemother., *11*:470, 1977
3. Antimicrob. Agents Chemother., *13*:584, 1978
4. Antimicrob. Agents Chemother., *12*:490, 1977
5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II 880. Washington, D.C.: American Society for Microbiology, 1978
6. Antimicrob. Agents Chemother., *13*:861, 1978
7. Data on file, Eli Lilly and Company
8. Principles and Practice of Infectious Diseases (edited by G.L. Mandell, R.G. Douglas, Jr., and J.E. Bennett), p. 487. New York: John Wiley & Sons, 1979

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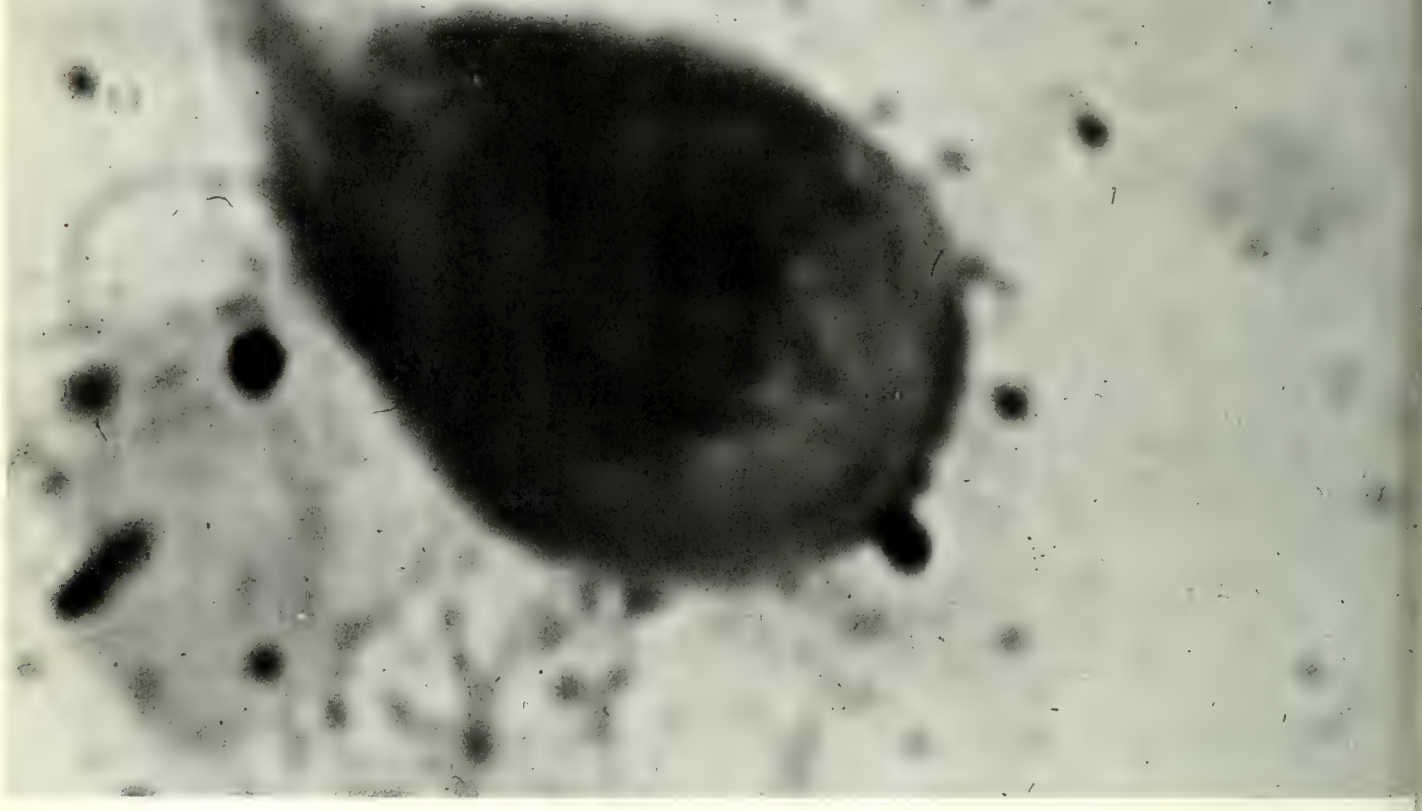

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Rosenthal, P., and Liebman, W.M: Comparative study of stool examinations, duodenal aspiration, and pediatric Entero-Test for giardiasis in children. *J. PEDIAT. 96:* 278 (Feb.) 1980.

Thomas, G. E., et al: Use of the Entero-Test duodenal capsule in the diagnosis of giardiasis. *South Afr. Med J. 48:* 2219, 1974.

Lopez, M. E., et al: Infeccion duodeno-yeyunal en el niño con desnutricion energetico-proteinica. *Rev. Med. Hosp. Nat. Niños 13:* 53, 1978.

Gilman, R. H: Identification of gall typhoid carriers by a string bladder device. *The Lancet:* April 14, p. 795, 1979.

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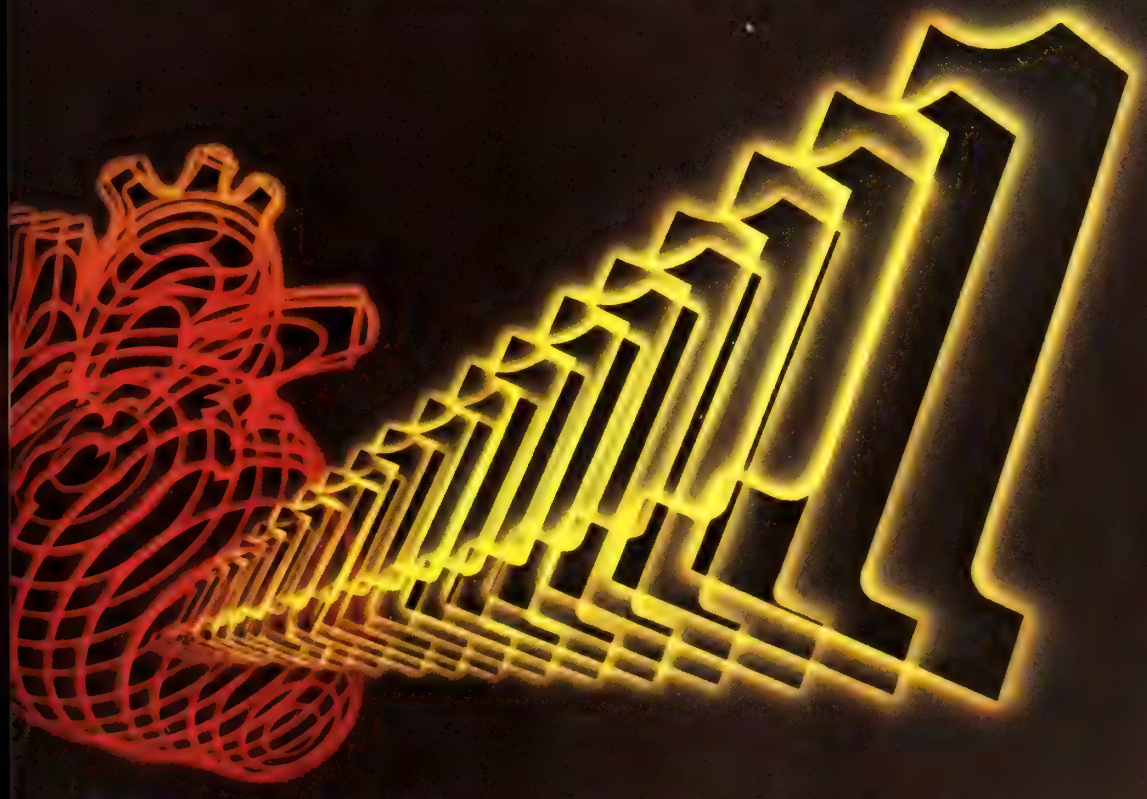

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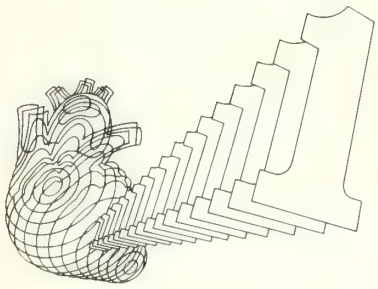

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WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occur commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 10 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 80 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

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375 *Announcement of the 78th Annual Meeting of the Nevada State Medical Association, Reno, May 14, 1982*

376 *Announcement of the 96th Annual Meeting of the New Mexico Medical Society, Santa Fe, May 5-7, 1982*

378 *In Memoriam*

Information for Authors, See March Issue, Advertising Page 36

Books Received, See Advertising Page 42

★ CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA; IDAHO; MONTANA; NEW MEXICO; OREGON; UTAH; WASHINGTON; WYOMING (See Advertising Page 35)

★★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

SPOT-RESISTANT
ORAL CONTRACEPTION
IS HERE!
It's LO/OVRAL 30. And here's how it holds spotting and breakthrough bleeding to a minimum: Hormone balance right from the start...and throughout the cycle. Hormone balance made possible with a very low dose oral contraceptive because of the supportive progestational activity of norgestrel, Wyeth's exclusive progestogen.
Regular withdrawal bleeding, too
despite its low dose. In clinical trials amenorrhea—defined as absence of bleeding in the 7 pill-free days—was reported in only 2.1% of total cycles. And when defined as absence of bleeding for 60 days or more (as it often is), the incidence was only 0.2%.*
And comfort for most patients*
thanks to the same balance that helps prevent spotting and breakthrough bleeding. In the clinical trials, most patients stayed free of common side effects such as nausea (0.6% of cycles), vomiting (0.1%), depression (0.5%) and acne (0.9%).
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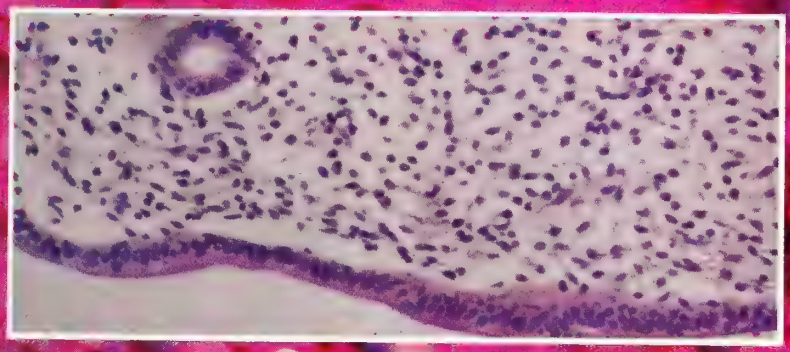
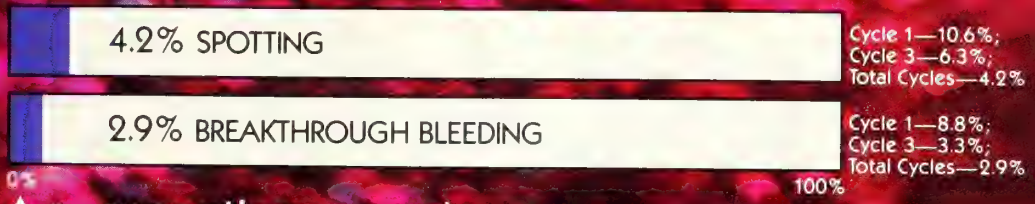


LO/OVRAL—1st cycle
Biopsy of intact endometrium in stable, progestogen suppressed state. Small, tubular gland in loose stroma without hemorrhage, fragmentation or debris characteristic of desquamating endometrium.

Even in the first cycle, the effective action of LO/OVRAL on the endometrium, such as you see here, provides the resistance against spotting and breakthrough bleeding you hope to achieve.

HISTOLOGICALLY... AND CLINICALLY.



A near-spotless record— in clinical trials involving 22,489 cycles*

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. Contraindications, Warnings, Precautions, Adverse Reactions, etc., in the accompanying In Brief should be carefully considered.

See full prescribing information.

LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth

...with a near-spotless record!

See important information on following page.

IN BRIEF:

Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3. Cerebral-vascular or coronary-artery disease
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia, papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's, clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's, effects if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion, change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum, cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates, vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

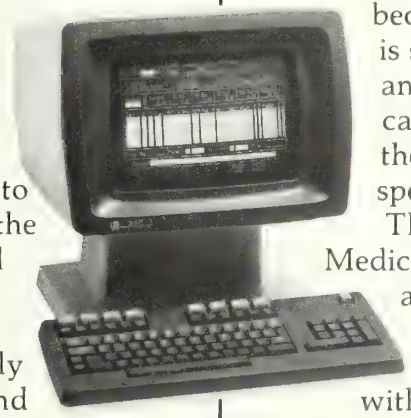
Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

LO/OVRAL® each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol

Wyeth Laboratories Phila., Pa. 19101

Why you should buy your medical computer system from a specialist instead of a general practitioner.

At Westland Medical Systems we do not try to be all things to all people.



We knew when we started that if we were going to be effective in the area of medical systems we would have to work intensively with doctors and only with doctors.

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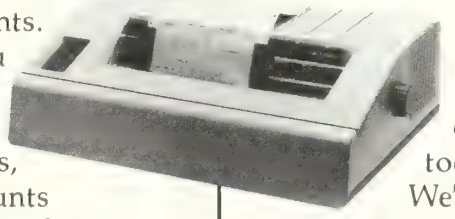
Before we ever designed our system we totally immersed ourselves in the business side of your practice. We learned how crippling paperwork can be. How delays in the preparation of insurance forms can seriously affect your cash flow. We learned how important it is for you to have your finger on your own financial pulse.

The result of all this learning was the Westland Medical System.

The Westland Medical System completely prepares all necessary insurance forms quickly and accurately so your turnaround time is as short as possible. And because our system is so flexible insurance information can be formatted to the needs of your specific practice.

The Westland Medical System issues all your patient statements and provides you with complete information about all outstanding accounts. It also gives you a number of valuable management reports, including accounts receivable age analysis, departmental revenue, and doctor productivity. All reports are available and updated on a daily basis.



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It does not require any special personnel. Instead of being written in Computerese it is written in easy to understand english sentences. Simple, step-by-step instructions direct the operator from the simplest (or most general) to the most detailed part of any task.

Your System can be set up and your people trained, in a matter of days. Best of all, this can be accomplished without interfering with the course of your work.

So why not call Westland today?

We'll specialize in your business so you can specialize in medicine.

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Motrin®

ibuprofen, Upjohn

600 mg Tablets

More convenient for your patients

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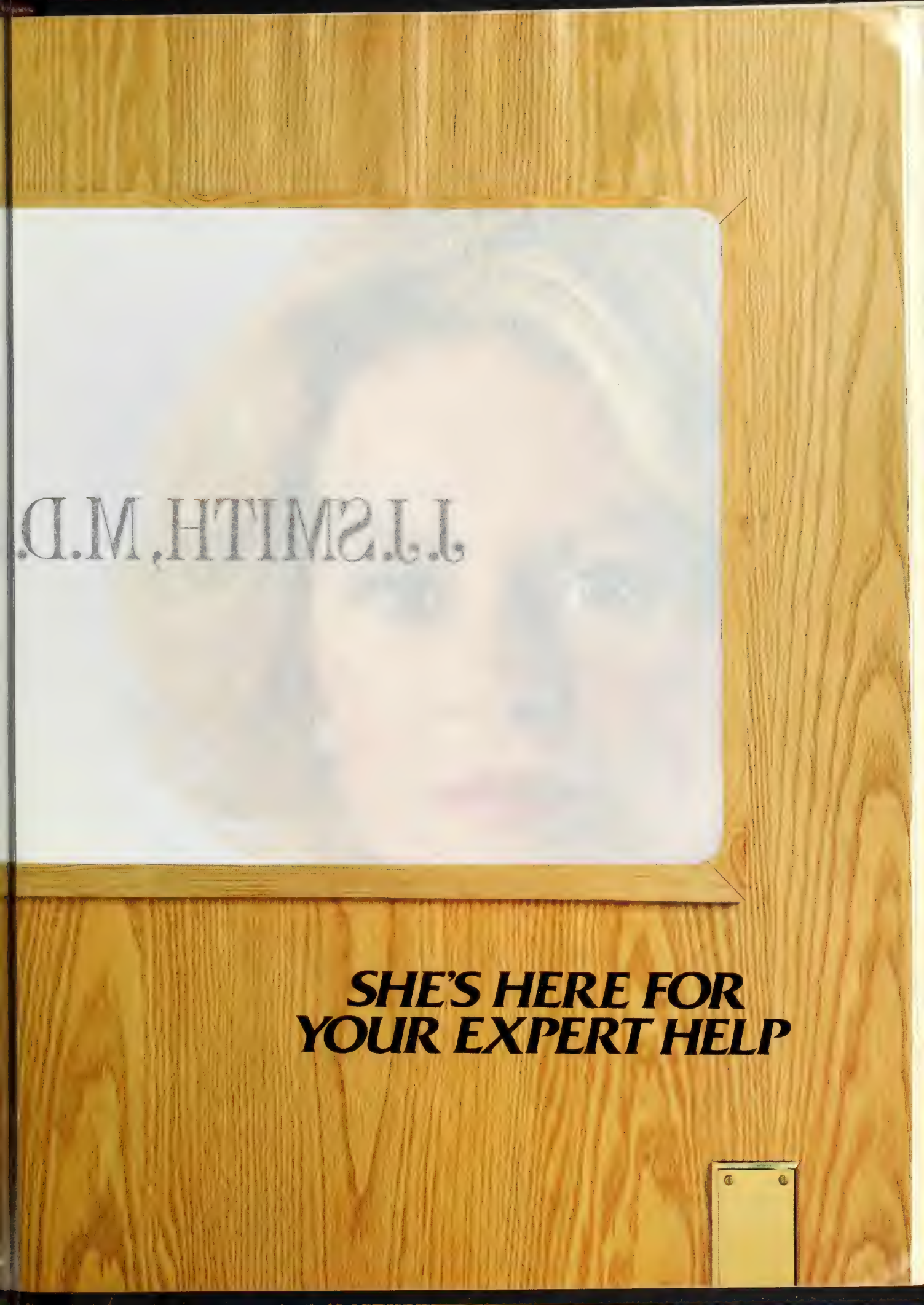
J-9043-4 July 1981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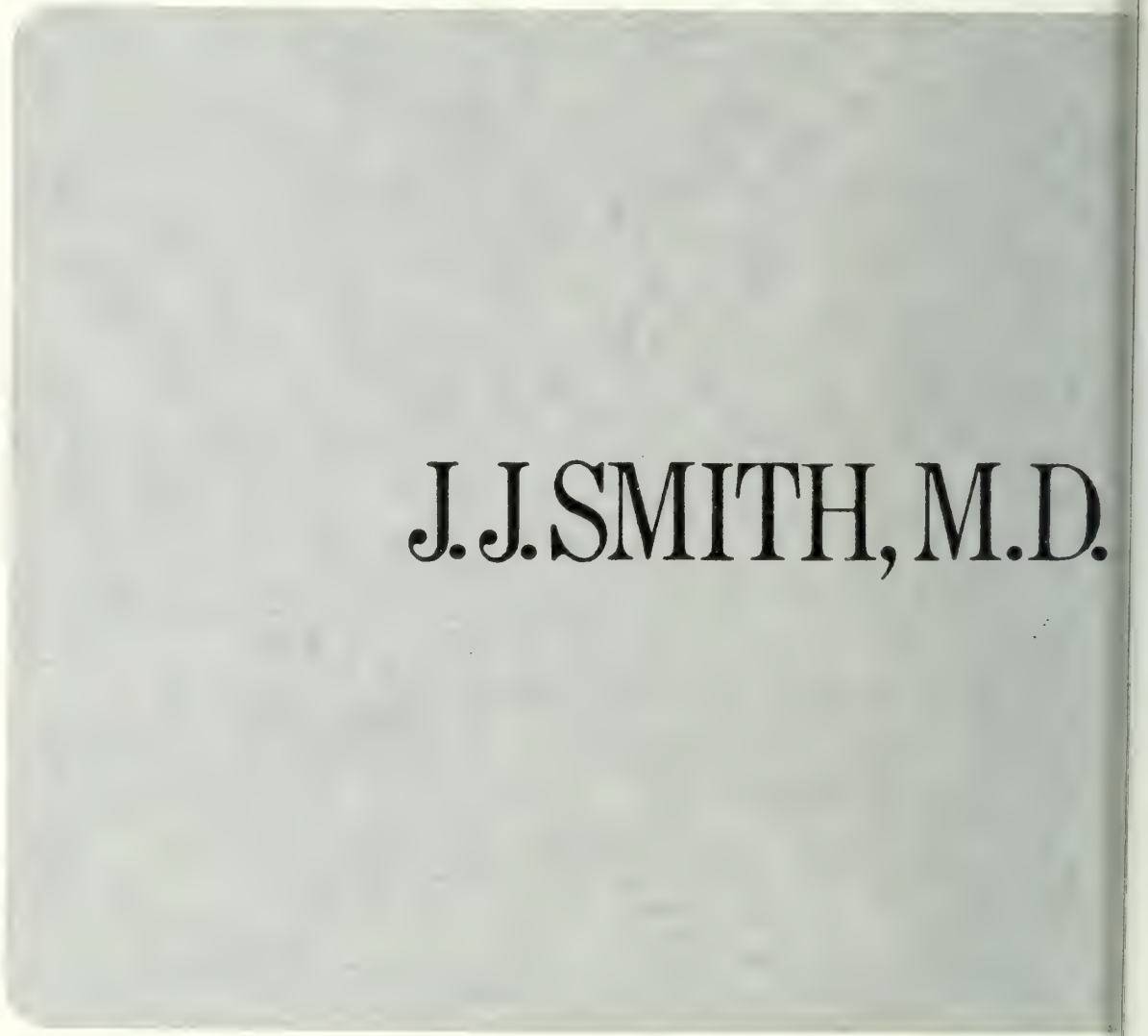
YOUR EXPERT HELP

COUNSELING MAY HELP HER CONCERNS



*For moderate to severe vasomotor symptoms, atrophic vaginitis, surgical menopause, postmenopausal osteoporosis†

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

Counseling. It can help the menopausal woman through this difficult time. But counseli can't stop the moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard postmenopausal osteoporosis† the way PREMARIN tablets can.

PREMARIN. It may slow the progression of osteoporosis.† It controls her embarrassing sweats and hot flushes. Relieves her discomfo Helps her cope.** PREMARIN is a useful adjunct in your expert management of her menopausal symptoms.

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IT PREMARIN® HELPS HER CONDITION*

If her menopausal symptoms are limited to
rophic vaginitis, you're aware of the rapid,
tually complete relief PREMARIN Vaginal
eam provides. In the properly selected patient,
not only relieves the distressing symptoms of
trogen deficiency, such as dyspareunia,
yness and itching, but it rebuilds vaginal tissue.
PREMARIN Vaginal Cream. You know what it
an do.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis.

There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms.

Please see following page for Brief Summary of Prescribing Information.

PHYSICIANS WHO CARE.

for atrophic vaginitis

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM

0.625 mg/gm

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease
8. Prostatic carcinoma - palliative therapy of advanced disease
9. Postpartum breast engorgement - Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day, comparable to those used to treat cancer of the prostate and breast) have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. With doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain, tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormally excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including contraceptives: breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis; change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.2 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically.* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer - 1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer; appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *brown* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. 872—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated applicator.

Also Available. Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube.

78

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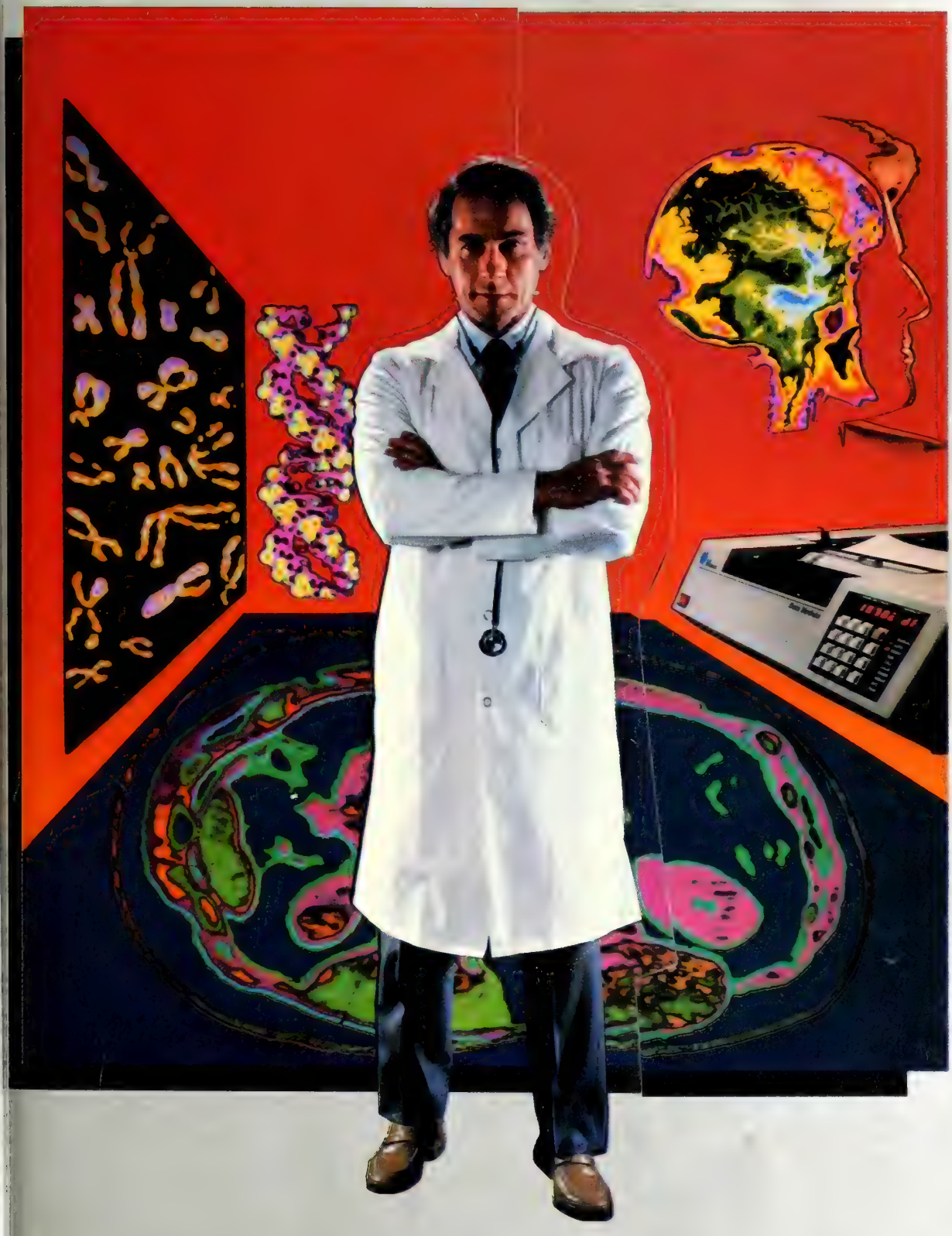
In an era of change,

An Agent of Change...



Your patients are changing

...the population is getting older, more peo
are holding a second job, patients are mo
concerned about the medications they ta

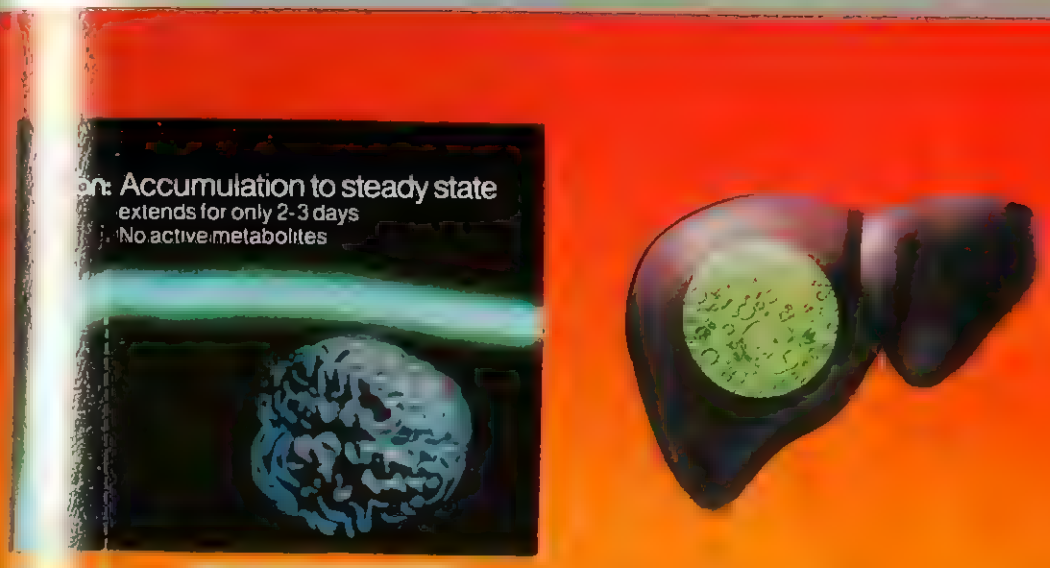
Medical knowledge is changing

...there are diagnostic resources and surgical techniques undreamed of only a few years ago, biomedical engineering, new insights also into the action of drugs.

In this changing environment, the way you are practicing medicine is changing too...

Twenty years ago, the benzodiazepine represented a real step forward in the management of anxiety and tension states. In recent years, however, concern about drug accumulation and clearance has led physicians to re-evaluate their use of these agents. In light of current knowledge, many clinicians are changing from multi-metabolite benzodiazepines to Ativan® (lorazepam)—a metabolically and pharmacokinetically distinctive agent that offers clinical advantages which more closely meet the expectations of a modern anxiolytic.

Ativan®: Agent of Change
(lorazepam)



because...

it's shorter acting, with less accumulation*

In contrast to long-acting benzodiazepines, Ativan has a short, 12-hour half-life, and no active metabolites. In multiple-dose therapy, Ativan accumulates for only two to three days before reaching steady state; the long-acting benzodiazepines—diazepam CIV, chlordiazepoxide CIV, clorazepate CIV and prazepam CIV—with their active metabolites—accumulate for as long as 20 days, increasing the likelihood of excessive sedation.

1. Klotz U, Reimann I: N Engl J Med *302*:1012-1014, 1980
2. Desmond PV, Patwardhan RV, Schenker S, et al: Ann Intern Med *93*:266-268, 1980
3. Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology *79*:912-916, 1980
4. Speilers EM, Naranjo CA, Peachey JE: N Engl J Med *305*:1255-1262, 1981
5. Ruffalo RL, Thompson JF, Segal JL: South Med J *74*:1075-1078, 1981

*Pharmacokinetics cannot as yet be directly related to efficacy

†Benzodiazepines produce additive effects when given with CNS depressants such as barbiturates or alcohol

it doesn't interact with drugs metabolized by P450 microsomal enzymes

Most benzodiazepines undergo oxidative metabolism and thus utilize the hepatic microsomal enzyme system. Ativan® (lorazepam), however, is metabolized by glucuronidation and does not compete with other drugs for cytochrome P450. Thus, when Ativan is given with Tagamet® (cimetidine), for example, clearance is not delayed, nor sedation increased†—unlike reported observations with patients on other benzodiazepines.[1-5]

it gives you greater control of therapy

The short half-life of Ativan® facilitates more rapid response to dosage adjustments, allowing you to titrate therapy to patients' changing needs. Also, once you decide to discontinue Ativan, it will be out of your patient's system four days after the final dose—in contrast to long-acting benzodiazepines and their active metabolites which take as long as two weeks to be totally eliminated.

Ativan®
for (lorazepam) IV
Anxiety

See important information on following page

Ativan®: Agent of Change
(lorazepam) ℞

- Little accumulation lessens likelihood of excessive sedation
- Unlike most benzodiazepines, Ativan does not compete with other drugs, such as Tagamet® (cimetidine), for the microsomal enzyme system during biotransformation
- Metabolism not affected by age or liver dysfunction
- Short half-life provides greater control of therapy
- Promptly eliminated from patient's system after discontinuation
- Specifically evaluated and found effective for anxiety associated with cardiovascular and gastrointestinal disorders
- A distinctive change from long-acting benzodiazepines, all of which have active metabolites and are much the same

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated; anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg or higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in

Adverse Reactions, if they occur, are usually observed during therapy and generally disappear on continued medication or decrease dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and dizziness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety

Overdosage: In management of overdosage with any drug, consider multiple agents may have been taken. Manifestations of overdosage somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis not been determined

Dosage: **Individualize for maximum beneficial effect. Increase dose gradually when needed, giving higher evening dose before bedtime, increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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UTAH-ANESTHESIOLOGIST: Growing area. Fee for Service. No neuro; no hearts. BE/BC only. Prefer United States, United Kingdom, Canadian trained. Send CV to: Ken Noel, MD, P.O. Box 839, Price, Utah 94501. (801) 637-5341 or (801) 637-4800.

OPHTHALMOLOGIST: Over 45, Wanted with interest in Medical Ophth, Peds/Strabismus, Plastics/Orbit or Neuro-Ophth. Dennis Shepard, MD, 1414 E. Main St., Santa Maria, CA 93454. (805) 925-2637.

PSYCHIATRIST, part-time position, 15-18 hours/week, flexible schedule possible, at Adult Outpatient Clinic. Please contact Gloria Gonzales, Assistant Director, Southeast Mental Health Center, 4190 Mission St., San Francisco, CA 94112. (415) 585-7753.

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HEMATOLOGIST-ONCOLOGIST WANTED—To join two others in well-established subspecialty practice in the Los Angeles area. Board certified or eligible. Excellent salary with unusual opportunity for early partnership. Inquiries and CV to Box 6282, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ORTHOPEDIC SURGEON—Position in Department of Orthopedics available July 1, 1982. 50-man multispecialty, fee-for-service group in San Diego. Interest in children's orthopedics and/or hand surgery preferred. Compensation guaranteed. Full partnership within two years. Please contact H. D. Peabody, Jr., MD, 2001 4th Ave., San Diego, CA 92101.

ORTHOPEDIC SURGEON—Board Certified or eligible, university trained orthopedic surgeon, preferably with additional specialty training (sports medicine, spine, joint replacement), to affiliate with an established orthopedic surgeon. Willing to wait for personable, experienced individual with commitment to patient care, research and teaching. New office building adjoining major hospital on the Palos Verdes Peninsula, California. Financial opportunity outstanding. Submit a CV and references to: James T. London, MD, 1360 West 6th St., Suite 305, San Pedro, CA 90732; (213) 833-2406.

ACADEMIC EMERGENCY DEPARTMENT DIRECTOR—Position available July 1, 1982 as Medical Director of Emergency Department, San Francisco General Hospital, an affiliated teaching hospital of the University of California, San Francisco. Emergency Department sees 75,000 patients yearly in medical, surgical, and ambulatory care areas, and functions as trauma center for San Francisco. Board Certification in emergency medicine, internal medicine, surgery, or other appropriate specialty required with at least 2 years experience in emergency medicine. The University of California is an Equal Opportunity Employer. Send curriculum vitae to Frank Lewis, MD, Emergency Department, San Francisco General Hospital, San Francisco, CA 94110.

GENERAL SURGEON—Board certified. Immediate income with unlimited opportunity to build practice. Exceptional promise for the very near future. To assist at surgery and share luxurious office with separate consultation rooms. Irving L. Lichtenstein, MD, 9201 Sunset Blvd., Los Angeles, CA 90069. (213) 274-3173.

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INTERNAL MEDICINE: Internist wanted for a large consultative practice in a beautiful rural area of northern California. Gross $8,000-$16,000 per month depending upon hours worked. Write or call: P.O. Box 3370, Clearlake, CA 95422. (707) 994-1028.

FAMILY PRACTICE ON PUGET SOUND: True comprehensive care in fantastic setting. Established clinic. Residency trained family practice seeking same. Must do OB. Salaried position with incentives. Starting date negotiable. Contact Gary A. Koch, MD, Vashon Health Center, P.O. Box 529, Vashon, WA 98070. (206) 463-3671.

SITUATIONS WANTED

BD CERTIFIED PEDIATRIC/ADULT ALLERGIST with 16 years teaching, private practive experience, FMG, financially secure, seeks California city of 40-60 k. Prefer solo practice but will consider loose association. Reply to Box 6290, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

(Continued on Page 28)

GASTROENTEROLOGIST

English/Spanish speaking. University trained in all procedures including ERCP, laparoscopy, manometry, etc. Currently Chief of GI Section in multispecialty clinic and hospital. Wish to relocate to California. Please reply to Box 6287, Western Journal of Medicine, 731 Market St., San Francisco, 94103.

ANESTHESIOLOGIST

Board certified Anesthesiologist for 140-bed teaching hospital affiliated with the University of California. In addition to attractive guarantee to cover administration, graduate training and critical care, the Physician is encouraged to establish a fee-for-service practice. Will be required to share weekend and evening coverage. Please submit curriculum vitae to:

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IN ANGINA PECTORIS*...

ISORDIL®
(ISOSORBIDE DINITRATE)

ACTIVITY RECONFIRMED BY THALLIUM SCINTIGRAPHY

How isosorbide dinitrate affects stress-induced abnormal myocardial perfusion in angina pectoris[1]

PROTOCOL
In 14 patients with coronary artery disease, thallium 201 scintigrams were obtained on appearance of angina pectoris during stress-testing and four hours after stress-testing, and then again four to six weeks later following a single 10 mg sublingual dose of isosorbide dinitrate (ISDN). In each patient six left ventricular segments were evaluated, for a total of 84 segments.

RESULTS
- Of 39 segments with exercise-induced perfusion defects, 25 were normalized after ISDN.
- ISDN reduced the segments with new or enlarged exercise-induced defects by 64%.
- ISDN increased the number of segments without new or larger stress defects by 55%.
- Angina and ST depression prevented in 11 of 14 patients.

CONCLUSION
The administration of ISDN results in a reduced but more homogeneous myocardial perfusion after stress, indicating a reduction in myocardial oxygen consumption. The authors believe this reduction reflects the peripheral action of ISDN.

ISORDIL (ISOSORBIDE DINITRATE) is prescribed today for approximately one out of every three angina patients.[2]

Available as:

ISORDIL SUBLINGUAL
Sublingual Tablets, 2.5 mg, 5 mg, and 10 mg

ISORDIL CHEWABLE
Chewable Tablets, 10 mg

ISORDIL TITRADOSE®
(E.Z. SPLIT®†) Oral Tablets, 5 mg, 10 mg, 20 mg, and 30 mg

ISORDIL TEMBIDS® Capsules and Tablets
Sustained-Action Capsules and Tablets, 40 mg

References
1. Wolf R, Pretschner P, Engels HJ, Hundeshagen H, Lichtlen PR: The effect of isosorbide dinitrate on stress-induced abnormal myocardial perfusion in coronary disease, substantiated by 201-thallium scintigraphy. *Zeitschrift für Kardiologie* 68:676-686, 1979.
2. Data on file, Ives Laboratories

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: When taken by the sublingual or chewable route, Isordil Sublingual and Chewable Tablets are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks

"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris

Final classification of the less-than-effective indications requires further investigation

Contraindication: Idiosyncrasy to this drug.
Warnings: Data supporting the use of nitrites and nitrates during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety
Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur. In patients with functional or organic gastrointestinal hypermotility or malabsorption syndrome, it is suggested that oral Titradose tablets, sublingual or chewable tablets, or Tembids **capsules** be the preferred therapy because a few patients have reported passing partially dissolved Tembids **tablets** in their stools. This phenomenon is believed to be on the basis of physiologic variability and to reflect rapid gastrointestinal transit of the tablet.
Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.
Consult direction circular before prescribing.

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(Continued from Page 26)

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CARDIOLOGIST—Board certified in medicine, CV Board taken. Well-trained and experienced in cath. and angioplasty plus noninvasive. Wishes to relocate. Will establish a cardiac cath. laboratory if necessary. Also licensed in California. Box 6288, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CONSCIENTIOUS CRITICAL CARE INTERNIST—28, seeks ICU staff position in San Francisco Bay Area. Board certified, with University Critical Care Fellowship. Substantial health policy/administration training including MBA. Willing to contribute to hospital administration activities. Available July 1982. Reply Box 6291, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

UROLOGIST—Desires to relocate from economically depressed Michigan town. 14 years solo experience. Board certified. Seek solo or association in city of less than 100,000 in any W or SW state. Bruce Knoll, MD, 707 N. Wisner, Jackson, MI 49202.

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RIMSO®-50
(dimethyl sulfoxide)
50% w/w aqueous solution

INDICATIONS AND USAGE

RIMSO® - 50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. RIMSO ® - 50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.

CONTRAINDICATIONS

None known.

WARNINGS

Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical RIMSO® - 50. The physican should be cognizant of this possibility in prescribing RIMSO® - 50. If anaphylactoid symptoms develop, appropriate therapy should be instituted.

PRECAUTIONS

Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of RIMSO® - 50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation.

Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO® - 50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide.

The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.

DOSAGE AND ADMINISTRATION

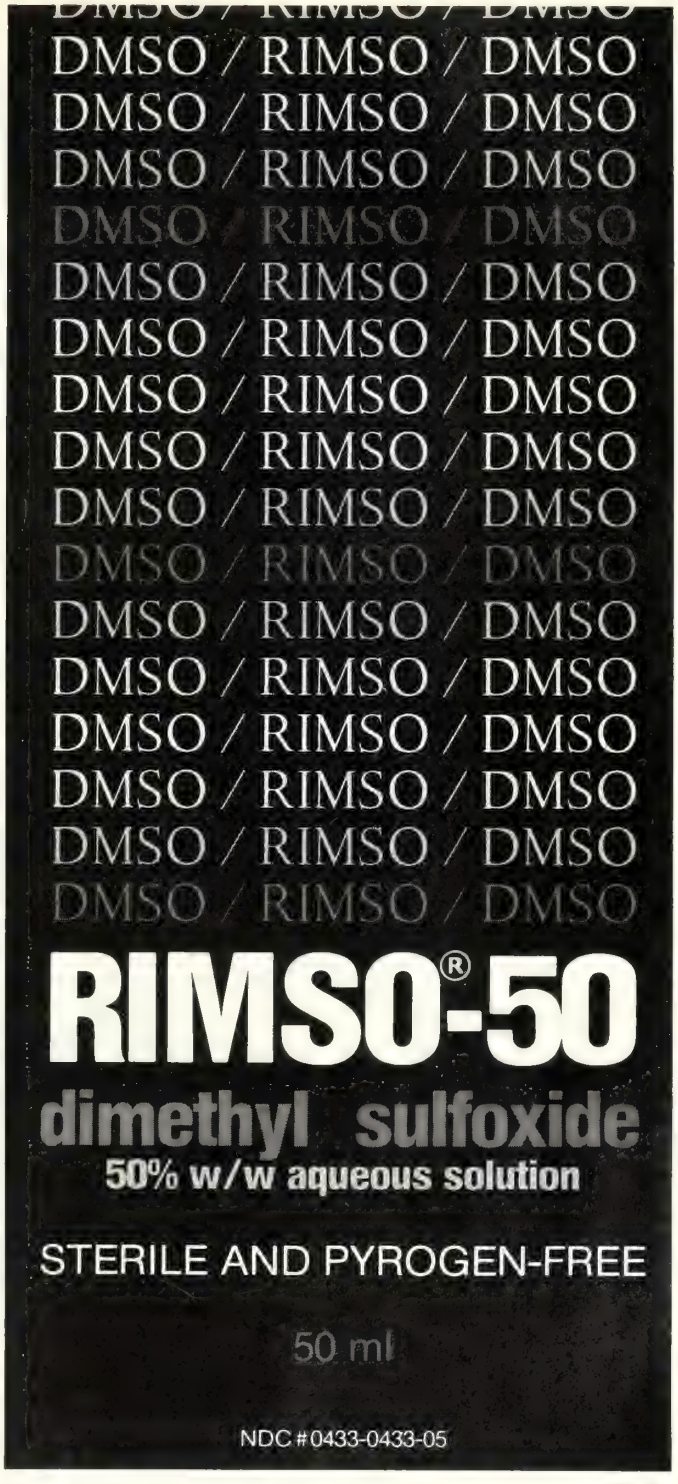
Instillation of 50 ml of RIMSO® - 50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as lidocaine jelly to the uretha is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately.

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO® - 50 can reduce bladder spasm.

In patients with severe interstital cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia. (Saddle block has been suggested).

HOW SUPPLIED

Bottles contain 50 ml of sterile and pyrogen-free RIMSO® - 50 (50% w/w dimethyl sulfoxide aqueous solution).
Dimethyl sulfoxide is clear and colorless.
Protect from strong light.
Store at room temperature (50° to 86°F) (15° to 30°C).
Do not autoclave.
NDC # 0433-0433-05



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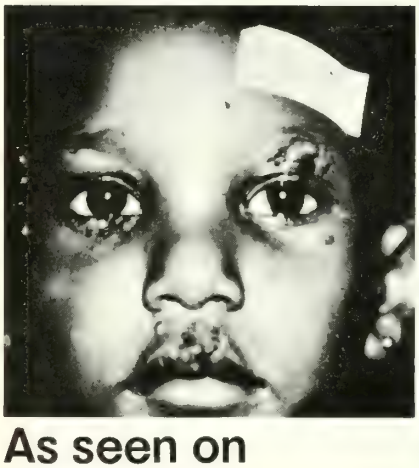

As seen on admission

After one week of penicillin V-K therapy

Two weeks after initiation of TEGOPEN therapy

Treatment failure was judged to have occurred when lesions increased in size and/or number during the initial week of treatment with penicillin V-K. *No* treatment failures occurred with Tegopen.

*Data on file, Bristol Laboratories.

Brief Summary of Prescribing Information

TEGOPEN®
(cloxacillin sodium)
Capsules and Oral Solution

For complete information, consult Official Package Circular. (12) 9/11/75

INDICATIONS:

Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed.

IMPORTANT NOTE

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

CONTRAINDICATIONS:

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication

RESULTS OF ORAL THERAPY revealed a high percentage of treatment failures with penicillin V potassium, but *no* failures with Tegopen.

		Given Tegopen® *(cloxacillin sodium)*	Given *penicillin V-K*
Staphylococcus aureus	(78 patients)	39	39
Returned to clinic at one week		29†	38†
Treatment failure at one week		0	18 (47.4%)
Staphylococcus aureus* and *Streptococcus pyogenes	(9 patients)	4	5
Returned to clinic at one week		4	5
Treatment failure at one week		0	2 (40%)
No initial bacterial growth	(14 patients)	9	5
All 14 healed, regardless of which antibiotic was administered.			
Beta-hemolytic *Streptococcus*	(1 patient)	0	1
TOTALS:	**102 patients**	**52 patients**	**50 patients**

†Eleven patients did not return for their one-week checkup These were all called by telephone, and their families reported the lesions had healed. One patient was dropped from the study, early, because of adverse reaction to medication

STUDY: DESCRIPTION/PROTOCOL

- 102 nonselected subjects, with initial bacteriology as follows: 77% *Staphylococcus aureus,* 9% mixed *Staphylococcus aureus* and *Streptococcus pyogenes,* and 1% beta-hemolytic *Streptococcus*.‡
- All patients were given randomized therapy—Tegopen capsules or oral solution, or penicillin V-K tablets or oral solution, in recommended dosages according to body weight.
- All patients were evaluated after one week's therapy. If there was no improvement, therapy was switched to the other antibiotic. The "other antibiotic" proved to be Tegopen 100% of the time because no treatment failures had occurred with Tegopen.
- A final assessment of progress was made two weeks after initiation of Tegopen therapy.

‡The remainder, to equal 100%, consisted of 14 patients (13%) who exhibited no initial bacterial growth. These 14 were all healed, whether given Tegopen or penicillin V-K

TEGOPEN®
(cloxacillin sodium)
–effective therapy for staph infections of the skin and skin structures

WARNING:
Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids

Safety for use in pregnancy has not been established

PRECAUTIONS:
The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

ADVERSE REACTIONS:
Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy

USUAL DOSAGE:
Adults: 250 mg. q.6h

Children: 50 mg./Kg./day in equally divided doses q.6h. Children weighing more than 20 Kg should be given the adult dose. Administer on empty stomach for maximum absorption.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS

SUPPLIED:
Capsules—250 mg. in bottles of 100. 500 mg. in bottles of 100.
Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles

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ANESTHESIOLOGY

April 26-30—**6th Annual Hawaiian Seminar on Clinical Anesthesiology.** Calif. Society of Anesthesiologists at Maui Surf Hotel, Maui. Monday-Friday. 20 hrs. Contact: Educational Programs Div., CSA, 100 E. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

May 22-23—**Hemodynamic Monitoring/Pulmonary Artery Catheterization—Hands-on Workshops.** Calif. Soc. of Anesthesiologists and Stanford at Stanford. Saturday-Sunday. 15 hrs. $275, CSA members; $325, nonmembers. Contact: Educational Prog. Div., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

June 10-13—**California Society of Anesthesiologists—Annual Meeting.** Town and Country, San Diego. Thursday-Sunday. Contact: Educational Prog. Div., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

June 24-26—**Practical Closed Circuit Anesthesia II.** Pacific Medical Center at Hyatt at Union Square, San Francisco. Thursday-Saturday. 17 hrs. $300. Contact: Office of Cont. Ed., PMC, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

August 13-17—**Clinical Neuroanesthesia Workshop.** UCSD at La Jolla Village Inn, La Jolla. Friday-Tuesday. 24 hrs. $325.

August 21-22—**Hemodynamic Monitoring/Pulmonary Artery Catheterization—Hands-on Workshops.** Calif. Soc. of Anesthesiologists and Stanford at Stanford. Saturday-Sunday. 15 hrs. $275, CSA members; $325, nonmembers. Contact: Educational Prog. Div., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

October 22-26—**American Society of Anesthesiologists.** Hilton, Las Vegas. Friday-Tuesday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

CANCER

April 15-17—**Cancer Symposium for Surgical and Medical Oncologists.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Saturday. 17 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 22-24—**Bladder Cancer.** American Urological Assn. at Biltmore Hotel, Los Angeles. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, AUA Office of Education, P.O. Box 25147, Houston, TX 77005.

May 7—**Lowell and Josephine Berry Oncology Seminar.** Bay Area Tumor Institute at Kaiser Center, Oakland. Friday. 8 hrs. Contact: Jeanne Hoek, (415) 465-8570.

June 18—**Symposium on Gynecologic Oncology.** Alta Bates Hospital, Berkeley. Friday. 7 hrs. $75. Contact: Med. Ed. Dept., Alta Bates Hosp., 3001 Colby St., Berkeley 94705. (415) 845-7110, ext. 2055.

October 1-2—**Advances in Heart Disease, Aging, Diabetes and Cancer Research.** See Medicine, October 1-2.

EMERGENCY MEDICINE

April 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMA, Inc., 2310 Mason St., San Francisco 94133. (415) 956-5900.

May 10-14—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD. Monday-Friday. 36 hrs. $425.

May 21-22—**Modern Concepts in Trauma Care.** Orange County Trauma Society and Mission Community Hospital at Disneyland Hotel, Anaheim. Friday-Saturday. 14 hrs. $195. Contact: John G. West, MD, Orange Co. Trauma Soc., 321 N. Rampart, Suite 120, Orange 92668. (714) 937-5030.

June 7-11—**Postgraduate Institute for Emergency Room Physicians—Symposium III.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs. $425.

(Continued on Page 39)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

BECAUSE A THIAZIDE ALONE CAN ONLY DO SO MUCH...

AND YET CAN DO TOO MUCH.

INCREASE CONTROL WITHOUT INCREASING POTASSIUM PROBLEMS.

A dependable means to long-term blood pressure control.

Many times, a diuretic alone can't keep hypertension in check. INDERIDE, however, can pick up where thiazide therapy leaves off.

The combination of propranolol HCl, the world's most trusted beta blocker, and hydrochlorothiazide, the standard among diuretics, enables INDERIDE to exert an additive antihypertensive effect.[1,2] In fact, a propranolol/hydrochlorothiazide regimen maintained blood pressure below 90 mm Hg in 81.8% to 86.4% of patients followed for 6 to 18 months of therapy.[1]

Low thiazide dosage means reduced risk of hypokalemia.

When thiazides are prescribed in doses greater than 50 mg/day, the potential for hypokalemia increases substantially. What's more, the greater the fall in serum K^+, the greater the risk of hypokalemia-induced PVCs.[3,4]

With INDERIDE, the additive hypotensive effect of propranolol HCl allows the effective dose of hydrochlorothiazide to be kept low (25 mg b.i.d.). And by lowering the daily dose of diuretic, INDERIDE also lowers the potential for diuretic-induced side effects. Potassium problems are less likely to occur—yet blood pressure can be controlled consistently.

INDERIDE®

Each tablet contains INDERAL® (propranolol HCl) 40 mg or 80 mg, and hydrochlorothiazide 25 mg

B.I.D. 40/25 80/25

When you know you need more than a thiazide.

Please see Brief Summary of Prescribing Information on following page.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)

INDERIDE®

BRAND OF
propranolol hydrochloride
(INDERAL®)
and hydrochlorothiazide

No 474—Each INDERIDE®-40/25 tablet contains
Propranolol hydrochloride (INDERAL®) 40 mg
Hydrochlorothiazide 25 mg
No 476—Each INDERIDE®-80/25 tablet contains
Propranolol hydrochloride (INDERAL®) 80 mg
Hydrochlorothiazide 25 mg

WARNING: This fixed combination drug is not indicated for initial therapy of hypertension Hypertension requires therapy titrated to the individual patient If the fixed combination represents the dosage so determined, its use may be more convenient in patient management The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant

DESCRIPTION: INDERIDE combines two antihypertensive agents INDERAL (propranolol hydrochloride), a beta-adrenergic blocking agent, and hydrochlorothiazide, a thiazide diuretic-antihypertensive

INDICATION: INDERIDE is indicated in the management of hypertension (See boxed warning)

CONTRAINDICATIONS: Propranolol hydrochloride (INDERAL®): Propranolol hydrochloride is contraindicated in 1) bronchial asthma, 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block, 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension, 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs

Hydrochlorothiazide: Hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to this or other sulfonamide-derived drugs

WARNINGS: Propranolol hydrochloride (INDERAL®): CARDIAC FAILURE. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i e* , that of supporting the strength of myocardial contractions) In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect The effects of propranolol and digitalis are additive in depressing AV conduction

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure In rare instances, this has been observed during propranolol therapy Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn, b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised Special consideration should be given to propranolol's potential for aggravating congestive heart failure Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm This is another reason for withdrawing propranolol slowly Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, *e g* , isoproterenol or levarterenol However, such patients may be subject to protracted severe hypotension Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e g.*, CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia This is especially important to keep in mind in patients with labile diabetes Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease In patients with renal disease, thiazides may precipitate azotemia In patients with impaired renal function, cumulative effects of the drug may develop

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma

Thiazides may add to or potentiate the action of other antihypertensive drugs Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported

USE IN PREGNANCY: Propranolol hydrochloride (INDERAL®): The safe use of propranolol in human pregnancy has not been established Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult

Nursing Mothers Thiazides appear in breast milk If the use of the drug is deemed essential, the patient should stop nursing

PRECAUTIONS: Propranolol hydrochloride (INDERAL®): Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals The drug should be used with caution in patients with impaired renal or hepatic function

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely hyponatremia, hypochloremic alkalosis, and hypokalemia Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids Medication such as digitalis may also influence serum electrolytes Warning signs, irrespective of cause are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or during concomitant use of corticosteroids or ACTH

Interference with adequate oral electrolyte intake will also contribute to hypokalemia Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability) Hypokalemia may be avoided or treated by use of potassium supplements such as foods with a high potassium content

Any chloride deficit is generally mild, and usually does not require specific treatment except under extraordinary circumstances (as in liver or renal disease) Dilutional hyponatremia may occur in edematous patients in hot weather, appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration

Thiazide drugs may increase the responsiveness to tubocurarine

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient Thiazides may decrease arterial responsiveness to norepinephrine This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy

Thiazides may decrease serum PBI levels without signs of thyroid disturbance

Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration, have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function

ADVERSE REACTIONS: Propranolol hydrochloride (INDERAL®): *Cardiovascular* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia; visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory bronchospasm

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous reversible alopecia Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol

Clinical Laboratory Test Findings Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

Hydrochlorothiazide: *Gastrointestinal* anorexia, gastric irritation, nausea, vomiting cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis

Central Nervous System dizziness, vertigo, paresthesias, headache, xanthopsia

Hematologic leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia

Cardiovascular orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics)

Hypersensitivity purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reaction

Other hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn

DOSAGE AND ADMINISTRATION: The dosage must be determined by individual titration (see boxed warning)

Hydrochlorothiazide is usually given at a dose of 50 to 100 mg per day The initial dose of propranolol is 40 mg twice daily and it may be increased gradually until optimum blood pressure control is achieved. The usual effective dose is 160 to 480 mg per day

One to two INDERIDE tablets twice daily can be used to administer up to 320 mg of propranolol and 100 mg of hydrochlorothiazide For doses of propranolol greater than 320 mg, the combination products are not appropriate because their use would lead to an excessive dose of the thiazide component

When necessary, another antihypertensive agent may be added gradually beginning with 50 percent of the usual recommended starting dose to avoid an excessive fall in blood pressure

OVERDOSAGE OR EXAGGERATED RESPONSE: The propranolol hydrochloride (INDERAL) component may cause bradycardia, cardiac failure, hypotension, or bronchospasm

The hydrochlorothiazide component can be expected to cause diuresis Lethargy of varying degree may appear and may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function, and in the absence of significant serum electrolyte changes or dehydration The mechanism of central nervous system depression with thiazide overdosage is unknown Gastrointestinal irritation and hypermotility can occur, temporary elevation of BUN has been reported, and serum electrolyte changes could occur especially in patients with impairment of renal function

TREATMENT: The following measures should be employed GENERAL—If ingestion is, or may have been, recent, evacuate gastric contents taking care to prevent pulmonary aspiration BRADYCARDIA—Administer atropine (0 25 to 1 0 mg) If there is no response to vagal blockade, administer isoproterenol cautiously CARDIAC FAILURE—Digitalization and diuretics. HYPOTENSION—Vasopressors, *e.g.*, levarterenol or epinephrine BRONCHOSPASM—Administer isoproterenol and aminophylline STUPOR OR COMA—Administer supportive therapy as clinically warranted GASTROINTESTINAL EFFECTS—Though usually of short duration, these may require symptomatic treatment. ABNORMALITIES IN BUN AND/OR SERUM ELECTROLYTES—Monitor serum electrolyte levels and renal function, institute supportive measures as required individually to maintain hydration, electrolyte balance, respiration, and cardiovascular-renal function

HOW SUPPLIED: *No 474*—Each INDERIDE®-40/25 tablet contains 40 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 and 1,000. Also in unit dose package of 100

No 476—Each INDERIDE®-80/25 tablet contains 80 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 and 1,000. Also in unit dose package of 100

References: 1. Veterans Administration Cooperative Study Group on Antihypertensive Agents J A M A. *237* 2303 (May 23) 1977 2 Bravo, E L , Tarazi, R C , and Dustan, H P N Engl J Med *292* 66 (Jan 9) 1975 3 Hollifield, J W , and Slaton, P E : Acta Med Scand [Suppl) *647* 67, 1981 4 Holland, O B , Nixon, J V , and Kuhnert, L Am. J Med. *70*:762 (Apr) 1981

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New York, N Y 10017

(Continued from Page 35)

une 28-July 2—**Topics in Emergency Medicine.** UCSF. Monday-Friday. 35 hrs. $350.

uly 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMA, Inc., 2310 Mason St., San Francisco 94133. (415) 956-5900.

August 9-13—**Postgraduate Institute for Emergency Room Physicians—Symposium II.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs.

September 13-17—**Postgraduate Institute for Emergency Room Physicians—Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 36 hrs.

September 28-October 1—**American College of Emergency Physicians.** San Francisco. Tuesday-Friday. Contact: ACEP, 3900 Capital City Blvd., Lansing, MI 48906.

October 11-15—**Postgraduate Institute for Emergency Room Physicians—Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 36 hrs.

October 22-24—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates, Inc., at Ralph W. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMA, 2310 Mason St., San Francisco 94133. (415) 956-5900.

October 25-29—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 35 hrs. $350.

MEDICINE

April 16—**Injectable Collagen—Applications and Technique.** STAN. Friday. $100. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

April 16-17—**Recent Advances in Renal, Metabolic and Endocrine Disorders.** St. Francis Medical Center at Bonaventure Hotel, Los Angeles. Friday-Saturday. $115. Contact: Allan M. Hoffman, EdD, Dir., Med. Ed., St. Francis Med. Ctr., 3630 E. Imperial Highway, Lynwood 90262. (213) 603-6171.

April 16-18—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

April 22-23—**Infectious Disease Symposium.** Epidemiology Assn. of Greater Sacramento and Mercy Hospital at Red Lion Inn, Sacramento. Thursday-Friday. 14 hrs. $90. Contact: Office of Cont. Med. Ed., Mercy General Hospital, 4001 J St., Sacramento 95819. (916) 453-4545.

April 25-28—**Dermatology.** UCD at Ahwahnee Hotel, Yosemite. One week.

April 28—**Thyroid '82.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Bonnie VanWaardenburg, Coordinator of Symposia, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

May 6-7—**Advances in Infectious Diseases.** UCSF. Thursday-Friday. 14 hrs. $170.

May 7-8—**Common Nervous System Pathology Diagnosis and Treatment.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 14 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 7-9—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

May 15—**Memory Loss—An Increasing Clinical Problem.** See Psychiatry, May 15.

May 15-18—**American Thoracic Society—Annual Scientific Meeting.** Bonaventure Hotel, Los Angeles. Saturday-Tuesday. 30 hrs. $35, members; $100, nonmembers. Contact: S. R. Iannotta, Exec. Dir., ATS, 1740 Broadway, New York 10019. (212) 245-8000.

May 17-21—**Advances in Internal Medicine.** UCSF. Monday-Friday. 40 hrs. $375.

May 21-22—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

May 27-30—**4th Annual Refresher Course in Allergy and Asthma.** UCD at Marriott's Great America, Santa Clara. Thursday-Sunday.

June 7-9—**Clinical Echocardiography—1982: M-Mode, 2-Dimensional and Pulse Doppler Techniques.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Monday-Wednesday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 9—**Bleeding Disorders.** LLU. Wednesday. 4 hrs. $30.

June 11-13—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Aladdin Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

June 25-27—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Newporter Inn, Newport Beach. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

July 10-18—**30th Annual Intensive Review of Internal Medicine.** USC. 9 days

July 16-17—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

July 17-24—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 21 hrs. $325.

August 6-8—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Clouds-Cal Neva Resort, Lake Tahoe. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 13-15—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 20-22—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at Hyatt, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 30-September 4—**Fifth Comprehensive Nephrology Review Course.** UCLA at Marriott, Los Angeles. Monday-Saturday. 28½ hrs. $595.

October 1-2—**Advances in Heart Disease, Aging, Diabetes and Cancer Research.** UCLA at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Robert J. Morin, MD, Harbor-UCLA Medical Center, Torrance 90509. (213) 533-2233.

October 6-10—**American Academy for Cerebral Palsy and Developmental Medicine—36th Annual Meeting.** Sheraton Harbor Island, San Diego. Wednesday-Sunday. 26 hrs. Contact: Kevin Johns, Convention Mgr., P.O. Box 11083, Richmond, VA 23230. (804) 355-9529.

October 9-16—**Gastroenterology.** USC at Mauna Kea Beach Hotel, Kamuela. One week.

October 21-23—**California Society of Internal Medicine—An-**

(Continued on Page 47)

In Hypertension*...When You Need to Conserve K+

Every Step of the Way

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K+ supplement or K+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K+ supplement or K+-sparing agent)

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Watch for signs of impending coma in severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia have been reported with thiazides. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide, dosage adjustments may be necessary. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluores cent measurement of quinidine. Hypokalemia is uncommo with 'Dyazide', but should it develop, corrective measure should be taken such as potassium supplementation c increased dietary intake of potassium-rich foods. Correctiv measures should be instituted cautiously and serum pota sium levels determined. Discontinue corrective measure and 'Dyazide' should laboratory values reveal elevated seru potassium. Chloride deficit may occur as well as dilution hyponatremia. Concurrent use with chlorpropamide ma increase the risk of severe hyponatremia. Serum PBI leve may decrease without signs of thyroid disturbance. Calciu excretion is decreased by thiazides. 'Dyazide' should b withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other an hypertensive drugs.

Diuretics reduce renal clearance of lithium and increase th risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizzines headache, dry mouth; anaphylaxis, rash, urticaria, pho sensitivity, purpura, other dermatological conditions, naus and vomiting, diarrhea, constipation, other gastrointestin disturbances; postural hypotension (may be aggravated alcohol, barbiturates, or narcotics). Necrotizing vascul paresthesias, icterus, pancreatitis, xanthopsia and respi tory distress including pneumonitis and pulmonary eder have occurred with thiazides alone. Triamterene has be found in renal stones in association with other usual calcu components. Rare incidents of acute interstitial nephritis a of impotence have been reported with the use of 'Dyazic although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Packag (unit-dose) of 100 (intended for institutional use only); Patient-Pak™ unit-of-use bottles of 100.

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THE WESTERN
Journal of Medicine

Refer to: Deffebach RR, Goodman RL, Miller L: Lumpectomy and irradiation in the treatment of early carcinoma of the breast. West J Med 1982 Apr; 136:281-286

Lumpectomy and Irradiation in the Treatment of Early Carcinoma of the Breast

ROY R. DEFFEBACH, MD, *Redwood City, California,* ROBERT L. GOODMAN, MD, *and* LEONARD MILLER, MD, *Philadelphia*

In the past two decades, the increasing ability of radiation to control local tumors in many organs, including the breast, has been well documented. In the past five years, the use of chemotherapy has also assumed a major role in treating micrometastases in breast cancer in selected premenopausal and postmenopausal patients. These two developments have forced a reappraisal of local modalities in the treatment of breast cancer.

Even before the advent of chemotherapy it was known that mastectomy alone was not successful in providing local control and thus adjunctive irradiation when axillae were histologically positive has been used to substantially reduce local recurrence rate. Studies now show that excisional biopsy followed by definitive irradiation accomplishes essentially the same local control, stage by stage, as mastectomy with adjunctive radiation therapy in selected cases. Also, similar five- and ten-year survival rates have been obtained in all recent series.

Irradiation appears to be at least comparable with mastectomy for control of cancer of the breast, but with better functional and cosmetic results.

CHANGING CONCEPTS in tumor biology and the development of new treatment modalities have generated an intense reappraisal of the standard therapies for early breast carcinoma, basically unchanged in the past 80 years. Increasing sophistication in all oncologic specialties now offers many patients with this disease equivalent probability of cure with avoidance of physical deformity and its concomitant psychological trauma.

Ionizing radiation has been used with increasing effectiveness as an anticancer agent since it was first used the year following Röntgen's discovery of x-rays. There are abundant data for a variety of tumor sites and types to indicate that doses of 4,400 to 5,000 rad in 4½ to 5½ weeks have an excellent probability of eradicating microscopic disease, and that doses of 6,600 to 8,000 rad in 6½ to 8 weeks will effectively destroy cancer cells

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ABBREVIATION USED IN TEXT

CMF = cyclophosphamide, methotrexate and 5-fluorouracil

in small lesions.[1] These observations, coupled with the prospect of preservation of normal functional anatomy, make primary radiation therapy the treatment of choice in many carcinomas of the head and neck, prostate and uterine cervix. It is hardly surprising that comparable doses have been found to be equally effective in the treatment of breast cancer.[2-4]

Changing Concepts

During the past 15 years, the concept of the natural history of breast cancer has changed dramatically. The idea that the tumor grew locally, then spread in a predictable fashion to regional lymph nodes and later metastasized hematogenously to distant sites underlay the halstedian principles of large en bloc resection. Throughout the first half of the century, a variety of local procedures were proposed to treat local disease and thereby improve cure; but in trial after trial, even with such procedures as the extended radical mastectomy, death rates stage for stage were depressingly consistent and highly correlated with axillary node status. In patients with apparently localized disease at initial therapy, 25 percent of negative-node and more than 60 percent of positive-node patients were dead of breast cancer in ten years.[5-10] Moreover, those patients who did not undergo en bloc resections seemed to fare no worse.[11]

Fisher was one of the first to recognize that breast cancer at the time of clinical presentation was often a systemic disease. Others became aware that nodal metastasis was a reflection of the host-tumor relationship and this awareness implied disseminated disease in a high proportion of patients.[12] The recent development of adjuvant chemotherapy directed against micrometastasis is a consequence of this thinking and appears to be favorably affecting ultimate survival.[7,13,14]

Traditionally, radiation therapy played an adjuvant role in the treatment of early breast cancer. It has over the years been administered preoperatively or postoperatively in combination with a variety of surgical procedures. The addition of postoperative irradiation in selected cases clearly reduces local recurrence in the chest wall several-fold from the generally reported incidence of 10 percent (stage T_1,* less than 2 cm) to 40 percent (stage T_3, greater than 5 cm) in histologically positive axillary groups where radical mastectomy only is done.[7,9] Adjunctive irradiation also probably increases the survival rate in those patients with positive internal mammary nodes, whether the lesion is located medially or laterally,[7,8] though large series are required to prove this.

With the introduction of systemic therapy in axillary-node-positive patients, the traditional indications for postoperative radiation therapy must be reconsidered, at least in clinical stages I and II.[13] The local recurrence rate with adjunctive chemotherapy without irradiation is possibly higher, but how much higher is still unclear. Our recommendations for postoperative radiotherapy have been modified when chemotherapy is planned, generally limited to those patients at a high risk of local recurrence (that is, where there are questionable or positive margins of resections, extension of tumor into axillary fat, known internal mammary lymph nodes or T_{3-4} primary lesions). In those patients in whom chemotherapy is not planned, usually in older postmenopausal women, irradiation is still recommended for T_2 and T_3 primary tumors, clinically or histologically positive nodes and histology grade 3 patients.

Effectiveness of Radiation Therapy

Radiation therapy as a primary treatment modality in breast cancer has a surprisingly long history. Geoffry Keynes[15,16] reported in 1929 and 1937 his results with interstitial radium. He was able to effect a five-year survival of 71 percent in 75 patients with disease confined to the breast and 29 percent in 66 patients with apparent axillary node involvement. Recognizing the difficulty in controlling large tumors, he later modified his regimen to include excisional biopsy of bulky masses. Baclesse[17] from the Foundation Curie published a remarkable article in 1949 reviewing his results of primary radiation using, by modern standards, primitive external-beam equipment (180 kV, 1 mm Cu filter). All of the 130 treated patients would today be considered to have advanced local disease. Not only did he bring about a 32 percent three-year disease-free overall survival, but he also documented control as a func-

*Based on TNM staging of tumors established by the International Union Against Cancer and the American Joint Committee for Cancer Staging and End Results Reporting (IUAC/AJC).

tion of dose and a greater degree of tissue tolerance with prolonged fractionation.

Over the last quarter century, increasing numbers of institutions have reported their experiences with radical radiotherapy. Initial interest was centered in Europe but more recently several American and Canadian groups have become very active. Specific techniques of radiotherapy have differed, as have the preirradiation surgical procedures, ranging from needle and incisional biopsy (Paris) to wedge mastectomy (Toronto).

The higher rate of local failure reported in the two French series[18,19] in which incisional biopsy only was done for tumor masses greater than 3 cm is almost certainly attributable to the presence of bulky disease at the initiation of radiation therapy. Ultimate survival at ten years may not be significantly worsened in these instances. Apparently the French school bases its practice on the belief that good cosmetic results cannot be achieved after removal of a large lump. It must be pointed out that the deformed fibrotic breast seen after the high dose necessary to eradicate such disease, or the defect left by subsequent operation, cannot be considered cosmetically ideal. In fact, excellent cosmetic results can be readily achieved after simple excision of T_2 and even selected T_3 tumors. Needle or incisional biopsy has been proved inadequate since the chest wall recurrence rate approaches that of mastectomy-only series.

With regard to radiotherapy techniques, a frequently cited clinical trial[20,21] completed ten years ago showed, for those with clinically positive axillary nodes, a higher local recurrence and lower survival rate with tylectomy (lumpectomy) and irradiation than with radical mastectomy plus postoperative irradiation. Even so, while using radiation dose levels suspected then and known now to be inadequate, and using orthovoltage equipment, ten-year survival comparable to surgical series was obtained with clinically negative, histologically positive axillary nodes.

Because local recurrence of breast cancer will show up in 75 percent of patients before three years and in 90 percent before five years, it would seem that this measurement would give a good early indication of the relative effectiveness of radiotherapy and surgery. Review of local recurrence data when currently acceptable radiation techniques are applied is quite instructive.[18,19,22-25] In these series, excisional biopsy followed by definitive radiation therapy yields a local recurrence rate of 3 percent to 5 percent at three years and 5 percent to 10 percent at five years for clinical stage I, and 7 percent to 10 percent at three years and 8 percent to 15 percent at five years for clinical stage II. In a carefully analyzed study,[26] it was shown that only 1 of 73 patients with tumors smaller than 5 cm (T_1 and T_2) had local recurrence with both excisional biopsy and interstitial irradiation boost, while 10 of 111 patients had recurrence when neither of these procedures was done. Both groups were followed a minimum of four years. In these series five-year survival without evidence of disease ranges from 85 percent to 90 percent for clinical stage I and 60 percent to 75 percent for clinical stage II. Most studies are single institution and nonrandomized, and few have substantial figures from follow-up over ten years. However, the National Surgical Adjuvant Breast Project (NSABP), the Cancer Institute of Milan and the National Institutes of Health have all instituted prospective randomized series comparing mastectomy with definitive irradiation.[27,28] Recently Veronesi of Milan and coworkers[29] reported equal five-year (90 percent) and seven-year (85 percent) survival for clinical T_1N_0 patients prospectively randomly selected to Halsted versus definitive radiation postexcisional biopsy and axillary dissection. Both groups received 12 cycles of cyclophosphamide (Cytoxan), methotrexate and 5-fluorouracil (CMF) if axillary nodes were positive. Their conclusion was firmly stated: "Radical mastectomy appears to involve unnecessary mutilation in (treatment of) carcinoma of the breast."

Evaluating Effectiveness of Therapies

In the evolution toward an effective method of controlling (curing) subclinical disease in distant areas, there has been an increasingly intense reassessment of current local and regional treatment techniques. Where mastectomy without adjunctive irradiation has been practiced, contending that immediate radiation does not improve survival, follow-up leads to certain conclusions. As discussed above, radical irradiation following lumpectomy shows local control comparable to radical mastectomy with selected adjunctive postoperative irradiation. When mastectomy is not followed by irradiation when there are positive axillary nodes, local recurrence ranges from 10 percent to 40 percent in the chest wall and 5 percent to 15 percent in the internal mammary and supraclavicular areas, depending on size of the

primary tumor and the number of nodes positive for metastasis. If local recurrence is two to four times more frequent with radical mastectomy alone (without adjunctive radio- or chemotherapy) than with radical radiotherapy, the burden of proof for treatment of choice rests on advocates of surgical management. A regional treatment method that is three times more effective in providing local control could not be less effective as a curative technique. Insistence on five-year survival rate comparison and, when these prove comparable, ten- and fifteen-year studies belies the importance of local recurrence rates when comparing local treatment techniques.

Any newly proposed therapy must also evaluate and compare morbidity and mortality. Radiation-induced carcinogenesis is extremely rare, occurring with less frequency than operative mortality from mastectomy, also quite rare. Significant morbidity immediately attendant with treatment is also unusual in both types of management. Therefore, immediate morbidity and mortality are not factors in deciding between the two treatment techniques. With approximate equivalents of morbidity and mortality, functional and cosmetic outcomes and cost and availability of resources become important considerations in evaluating which treatment to use in a given clinical situation. From evaluation of available data, minimal surgery followed by definitive irradiation can meet these basic needs.

Critically important is the patient's own treatment preference, ideally established after a balanced discussion with one or more physicians knowledgeable about the various treatment approaches. While most patients would much prefer to retain their breast, there are some who would suffer continuing anxiety should the cancerous breast not be removed. A few would rather undergo a less time-consuming and inconvenient procedure than radical irradiation. In still others with moderately advanced local disease but still in the absence of known dissemination, both rigorous irradiation and radical surgical intervention may be required.

Choosing Biopsy Plus Irradiation

The decision for choosing either mastectomy or irradiation should be based primarily on subsequent appearance of the breast. Stage T_1 and T_2 (less than 5 cm in diameter) and selected T_3N_0 and N_1 disease are appropriate for irradiation unless the breast is so small in relation to tumor size that lumpectomy alone would leave a cosmetically deformed breast. Surgical operation, while both diagnostic and therapeutic in this type of management, should consist of a "debulking" procedure. Excisional biopsy to establish the diagnosis of cancer is followed by a metastatic workup, including complete blood count (CBC), liver function test, chest x-ray studies and bone scan. Preoperative bilateral mammograms and postbiopsy mammograms of the involved side are necessary if there is any question of residual tumor. Whenever possible, the biopsy should be a total excision of tumor, but it is not necessary to obtain a wide margin of resection. On the contrary, the smallest possible amount of tissue that includes the mass should be taken to achieve the best cosmetic result. When frozen section diagnosis confirms the presence of a malignant lesion, sampling of the lowest level of axillary nodes can be done through a small separate incision, under the same anesthesia, removing those nodes lateral to the pectoralis minor. Sampling of axillary nodes will not interfere with mastectomy if this approach is later selected and will help in radiation therapy planning and in considering adjuvant chemotherapy; it can also provide an indication of ultimate prognosis. If a patient is of an age and medical condition where adjuvant chemotherapy cannot be administered, axillary sampling may be omitted in clinical N_0 patients, though it does provide valuable prognostic information. Estrogen receptors are obtained from the biopsy specimen. When all of the above have been accomplished, the physician can then discuss treatment alternatives with the patient.

The above approach reflects an important transition in the United States in the evaluation of patients with a breast mass. In most centers around the country, 80 percent of biopsied masses prove to be benign. The one-stage procedure (when mastectomy immediately follows frozen-section confirmation of malignant disease) precludes patient involvement in the decision for type of treatment, prevents adequate evaluation of extent of disease and subjects all patients with a breast lump to uncertainty over possible loss of the breast. Unequivocal proof exists that a two-stage surgical procedure will not result in a lower survival rate or higher incidence of local recurrence.

If radiation therapy is selected, ten days to two weeks are allowed for healing, and treatment is then begun. As mentioned above, with mastec-

tomy-only series the supraclavicular and internal mammary node recurrence rate is 5 percent to 15 percent (higher if the primary is in the medial half of the breast) when the axillary nodes are histologically positive; in these situations we recommend radiation of these lymph node chains. The patient is administered 4,400 to 5,500 rad to the entire breast through opposing wedged tangential fields. This technique ensures a homogeneous dose distribution through the treatment volume. If it is to be treated, the internal mammary chain may be included in the tangential or the supraclavicular field. A bolus of up to 1,000 rad may be administered to the breast to bring the 100 percent dose to 3 mm below the skin, but more than this will compromise cosmetic appearance and should be avoided unless there is direct extension of tumor to the skin. Axillary and supraclavicular areas are treated by an anterior field angled off the spinal cord and thoracic spine if treated with photons, at 160 to 190 rad a day to a dose of 4,400 to 4,600 rad at a depth of 5 cm, occasionally supplemented by a posterior axillary boost. Electrons of varying energy levels may be used for the various fields, either in combination with photons or alone.

One to two weeks after external irradiation is completed, patients should have iridium 192 implantation under either local or general anesthesia. The implant volume is determined by breast size and initial tumor size. A dose of 1,500 to 2,500 rad is delivered to the implanted area. Some centers prefer electron boost and report similarly acceptable cosmetic results. In the United States iridium is more widely available than electrons and the implantation technique is easily mastered. Complications of technically meticulous radiation therapy have been minimal. They consist of occasional lymphedema of the arm or breast or both (occurring most frequently in conjunction with unnecessarily extensive axillary node dissection), radiation pneumonitis and rib fractures.

Potentially of great importance, whether surgical therapy or irradiation is used, is the effect of systemic chemotherapy on local control. In Bonadonna and colleagues' initial report[13] of CMF as adjuvant treatment following radical mastectomy in patients with primary breast cancer and positive axillary nodes, the reported incidence of regional recurrence was 9.4 percent in 179 control patients, as compared with 1.9 percent in 207 CMF patients. While patient selection is apparent because the local recurrence rate from radical mastectomy only from the same institution[7] in earlier series was 25 percent to 30 percent, it is clear that chemotherapy reduces the incidence of local recurrence. More recent reports indicate that CMF therapy after mastectomy yields a slightly higher local recurrence rate than with irradiation therapy after mastectomy, but the implication of these newer data remains to be determined.

If there are positive nodes, adjuvant CMF chemotherapy may be administered. Because of recent data indicating that postmenopausal patients who receive full doses of drugs show a similar response to adjuvant chemotherapy as premenopausal patients, drugs are prescribed in younger postmenopausal women who are in generally good health.

Early exposure to the drug is also considered to be important. Several alternatives for sequential or concomitant radiation and chemotherapy are available. Some give two cycles of full CMF before irradiation, followed after radiation recovery by ten more cycles. Others use full-dose cyclophosphamide and 5-fluorouracil at the initiation of x-ray therapy, with methotrexate added after completion of irradiation, and still others begin with both full-dose CMF and irradiation, generally with the latter avoiding the thoracic column and with lower daily dose rates (for example, 160 rad). In all cases, a full-dose 12-cycle CMF course is delivered if at all possible. The phenomenon of additive toxicities is not entirely clear and there must be close clinical scrutiny during this combined-modality treatment regimen. However, the role of irradiation in lowering total feasible dose of chemotherapy when applied carefully is probably marginal and should not be used as a justification for mastectomy in place of irradiation where systemic chemotherapy is anticipated. Carefully coordinated irradiation and drug therapy will enable the optimum benefits of both to be realized.

Certainly a number of issues remain concerning radical irradiation as an alternative to mastectomy in early breast cancer. In particular, the amount of breast tissue removed, the necessity for and type of booster dose, the extent of axillary node dissection and the influence of chemotherapy on local control are undergoing evaluation. However, the local control following lumpectomy, axillary node sampling and radical irradiation has been found so effective that where appropriate radiation oncology skills are available, this pro-

cedure is an alternative preferable to radical mastectomy, will not compromise a patient's chance for survival and will leave a patient in almost all cases without cosmetic or functional morbidity.

REFERENCES

1. Fletcher GH: Clinical dose response curves of human malignant epithelial tumors. Br J Radiol 1973 Jan; 46:1-12

2. Fletcher GH: Local results of irradiation in the primary management of localized breast cancer. Cancer 1972 Mar; 29: 545-551

3. Ghossein NA, Stacey P, Alpert S, et al: Local control of breast cancer with tumorectomy plus radiotherapy or radiotherapy alone. Radiology 1976 Nov; 121:455-459

4. Montague ED, Gutierrez AE, Baker JL, et al: Conservation surgery and irradiation for the treatment of favorable breast cancer. Cancer 1979; 43:1058-1061

5. Fisher B, Slack NH, Cavanaugh PJ, et al: Postoperative radiotherapy in the treatment of breast cancer: Results of the NSABP clinical trial. Ann Surg 1978; 172:711-732

6. Easson EC: Post-operative radiotherapy and breast cancer, *In* Prognostic Factors in Breast Cancer. Edinburgh, Livingston, 1968, pp 118-127

7. Valagussa P, Bonadonna G, Veronesi U: Patterns of relapse and survival following radical mastectomy. Cancer 1978; 41:1170-1178

8. Urban J, Castro EG: Selecting variations in extent of surgical procedure for breast cancer. Cancer 1971; 28:1615-1623

9. Donegan WL: The influence of untreated internal mammary metastasis upon the course of mammary cancer. Cancer 1977; 39:353-538

10. Haagensen CD (Ed): Diseases of the Breast. Philadelphia, W. B. Saunders, 1971, pp 704-734

11. Fisher B, Montague E, Redmond C, et al: Comparison of radical mastectomy with alternative treatments for primary breast cancer—A first report of results from a prospective randomized clinical trial. Cancer 1977 Jun; 39(Suppl 6):2827-2839

12. Fisher B: Breast-cancer management: Alternatives to radical mastectomy (Sounding Board). N Engl J Med 1979 Aug 9; 301:326-328

13. Bonadonna G, Brusamolino E, Valagussa P, et al: Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976; 294:405-410

14. Bonadonna G, Valagussa P: Dose-response effect of CMF in breast cancer. Proceedings of the American Society of Clinical Oncologists 1980; 21:413

15. Keynes G: The treatment of primary carcinoma of the breast with radium. Acta Radiol 1929; 10:393-402

16. Keynes G: Conservative treatment of cancer of the breast. Br Med J 1937; 2:643-647

17. Baclesse S: Roentgen therapy as the sole method of treatment of cancer of the breast. Am J Roentgenol 1949; 62:311-319

18. Calle R, Pilleron JP, Schlienger P, et al: Conservative management of operable breast cancer: Ten years experience of the Foundation Curie. Cancer 1978 Oct; 42:2045-2053

19. Pierquin B, Owen R, Maylin C, et al: Radical radiation therapy of breast cancer. Int J Radiat Oncol Biol Phys 1980 Jan; 6:17-24

20. Atkins H, Hayward JL, Klugman DJ, et al: Treatment of early breast cancer: A report after ten years of clinical trial. Br Med J 1972; 2:423-429

21. Hayward JL: The Guy's trial of treatment of "early" breast cancer. World J Surg 1977; 1:314-316

22. Proznitz LR, Goldenberg IS, Packard RA, et al: Radiation therapy as initial treatment for early stage cancer of the breast without mastectomy. Cancer 1977; 39:917-923

23. Alpert S, Ghossein NA, Stacey P, et al: Primary management of operable breast cancer by minimal surgery and radiotherapy. Cancer 1978; 42:2054-2058

24. Peters MV: Cutting the Gordian knot in early breast cancer. Ann R Coll Phys Surg Can 1975; 8:186-192

25. Bedwinek JM, Brady L, Perez CA, et al: Irradiation as the primary management of stage I and II adenocarcinoma of the breast: Analysis of the RTOG breast registry. Cancer Clin Trials 1980 Spring; 3:11-18

26. Harris JR, Levene MB, Hellman S: The role of radiation therapy in the primary treatment of carcinoma of the breast. Semin Oncol 1978 Dec; 5:403-416

27. Veronesi U: Conservation treatment of breast cancer: A trial in progress at the Cancer Institute of Milan. World J Surg 1977 May; 1:324-326

28. Fisher B: United States trials of adjuvant surgery. World J Surg 1977 May; 1:331-335

29. Veronesi U, Saccozzi R, del Vecchio M, et al: Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med 1981 Jun 2; 305:6-11

Refer to: Blaser MJ, Reller LB, Luechtefeld NW, et al: *Campylobacter* enteritis in Denver. West J Med 1982 Apr; 136: 287-290

Campylobacter Enteritis in Denver

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To determine the relative importance of Campylobacter jejuni *as a cause of diarrheal illness in patients coming to three hospitals in Denver, we cultured stool specimens from 2,670 patients over a two-year period.* C jejuni *was identified in the feces of 124 patients (4.6 percent),* Salmonella *from 90 (3.4 percent) and* Shigella *from 77 (2.9 percent). Most* Campylobacter *isolates were obtained in the summer months and from patients 10 to 29 years old. The illness usually lasted less than two weeks; predominant symptoms were diarrhea (98 percent), abdominal pain (88 percent) and fever (82 percent); patients with severe illness frequently had objective evidence of nonspecific colitis. Occult blood and leukocytes were present in stool specimens of 71 percent and 85 percent, respectively, of the patients tested. The duration and severity of illness led to antibiotic therapy in about half of the patients; erythromycin appeared effective. This study confirms the importance of* C jejuni *as a cause of enteritis; this microorganism should be sought routinely in fecal specimens from patients with diarrhea.*

Campylobacter jejuni is being recognized with increasing frequency as an enteric pathogen of humans.[1-8] Studies on all continents and in varied climates[2-8] have shown that *C jejuni* is a ubiquitous microorganism; however, the epidemiology of *Campylobacter* enteritis and its clinical features are still being defined.

To delineate the clinical and epidemiologic features of *Campylobacter* infection, we collected data on all patients from whom *C jejuni* was isolated at three large Denver hospitals. The results of the first six months of those studies have been reported[8]; we now present data from two full years of surveillance that extend the original findings. During the two-year period of study, *C jejuni* infection was more common than either *Salmonella* or *Shigella* infection, with a distinct age and seasonal distribution.

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Materials and Methods

The study included stool specimens from all patients whose physicians requested culture for enteric pathogens at the three collaborating hospitals from March 1978 through February 1980.[8] In addition to conventional media for isolating *Salmonella* and *Shigella*,[9] a selective plate medium

(Campy-BAP) was used and incubated as described previously.[8] All fecal specimens were cultured within two hours of receipt. Colonies with typical morphology for *Campylobacter* on the Campy-BAP were examined and *C jejuni* was identified according to standard criteria.[8] Rotaviruses, *Yersinia enterocolitica* and *Clostridium difficile* were not sought. Parasitology tests, complete blood counts and blood chemistry determinations were done when requested by the primary physician.

All patients from whom fecal material was obtained were classified as to age, sex, date of submission of the specimen and pathogens found. The hospital chart of every patient with *Campylobacter* infection was reviewed and the patients or their parents were interviewed by one of us whenever possible. Complete histories were taken that emphasized the course and clinical features of the illness.

Results

Epidemiologic Findings

During the two years a total of 2,670 fecal specimens were cultured at the three hospitals; *Campylobacter* was isolated from 124 (4.6 percent), *Salmonella* from 90 (3.4 percent) and *Shigella* from 77 (2.9 percent). Four patients had mixed infections: two with *Campylobacter* and *Salmonella,* one with *Campylobacter* and *Shigella* and one with *Campylobacter, Shigella* and *Giardia lamblia.*

More *Campylobacter* isolates were found in stool specimens in the warmer months (May through August) than in the cooler months (December through March)—both in absolute numbers and as a percentage of cultures done (Figure 1). No such seasonal pattern was observed for *Salmonella* or *Shigella.* No increase was observed in the number of specimens obtained from young children during the winter months. The rates at which *Campylobacter* was isolated from male patients (5.2 percent) and female patients (4.0 percent) were not significantly different. Most *Campylobacter* isolates were obtained from older children and young adults (Table 1). *Campylobacter* was isolated from 8.4 percent of patients 10 or more years of age but from only 2.0 percent of those under 10 ($x^2 = 56.6$, $P < .001$). In contrast, for *Salmonella* the highest age-specific isolation rate was for patients less than a year old and for *Shigella* it was for those from ages 1 through 9. For male patients 10 through 29 years of age whose specimens were cultured in the period June through September, the isolation rate for *Campylobacter* was 21.9 percent; for female patients of that age group the comparable rate was 18.1 percent.

Clinical Features of Campylobacter Infection

Symptoms. A prodrome of one or more days of malaise, myalgia, headache and fever was noted by 18 percent (22/124) of patients. For 62 percent of the patients the onset of illness was sudden, with abdominal cramps and diarrhea often severe enough to wake them from sleep. The symptoms noted when the patients were seen initially at the hospital are shown in Table 2. Studying the group of patients who had stool specimens taken for culture biases the results toward persons with diarrhea; nonetheless *Campylobacter* was identified from three patients who had no diarrhea. Two of them had specimens taken for culture because of sudden abdominal pain and fever, and one infant had a culture done after she passed a grossly bloody stool. Two thirds of the patients had eight or more bowel movements on the worst day of the

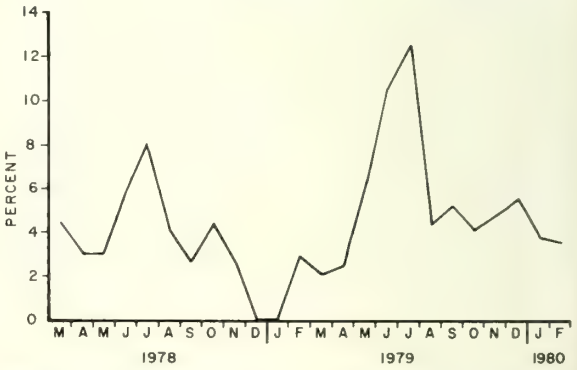

Figure 1.—Rate of isolation of *Campylobacter* from fecal specimens at three Denver hospitals by month, March 1978 through February 1980.

TABLE 1.—*Rate of Isolation of Three Enteric Pathogens From Fecal Specimens Submitted to Three Denver Hospitals by Age of Patient, March 1978 Through February 1980*

Age (yr)	Number of Fecal Specimens	Positive Fecal Specimens (%)		
		Campylobacter	*Salmonella*	*Shigella*
<1	875	12(1.4)	35(4.0)	2(0.2)
1-9	656	20(3.0)	19(2.9)	45(6.9)
10-29	554	68(12.3)	20(3.6)	17(3.1)
30-49	252	17(6.7)	5(2.0)	8(3.2)
50-69	204	6(2.9)	4(2.0)	0(0.0)
>70	73	1(1.4)	3(4.1)	3(4.1)
Unknown	56	0(0.0)	4(7.1)	2(3.6)
TOTALS	2,670	124(4.6)	90(3.4)	77(2.9)

TABLE 2.—*Symptoms of 124 Patients With Campylobacter enteritis Seen at Three Denver Hospitals*

Symptom	All Patients	Percentage With Symptom: Children (<10 yr) (n=31)	Percentage With Symptom: Older Children and Adults (n=93)
Diarrhea	98		
Defecation ≥8 on worst day	65	45†	71†
Gross blood present	52	48	53
Bile-stained stools	36		
Mucus in stools	35		
Malaise*	95		
Abdominal pain*	88		
Fever	82	57†	91†
Nausea*	55		
Vomiting	35	33	35

*Could not be evaluated for very young children. For these symptoms, n=110 patients.
†$P < .01$.

illness and about half noted gross blood in their stool.

Cramping abdominal pain, either periumbilical or involving the lower quadrants, frequently was noted. Nausea and vomiting rarely were the principal features of the illness but generally accompanied the most severe stages of cramping and diarrhea. Abdominal distention and tenesmus were rare complaints. Most patients had anorexia; however, almost all those who were ill for less than a week lost less than 2.3 kg (5 lbs).

Those who reported having fever said it was present either before the onset of the gastrointestinal symptoms or coincident with the first two days of diarrhea. Of patients under age 1, 36 percent had a history of fever, as did 68 percent of those 1 to 9 years old and 91 percent of those over 10 years old. Persistent fever was unusual but was reported by those patients with the most severe enteric symptoms. Rigors, noted by 10 percent of patients, occasionally heralded the onset of illness. Headache, backache, myalgia and arthralgia were each reported by less than 30 percent of patients; frank arthritis was not noted.

Signs and laboratory findings. The initial physical examination of the patients and the related laboratory findings usually were normal or nondiagnostic. Eight patients had postural changes in their blood pressure and pulse, but no other signs of dehydration were seen. Fever (temperature of greater than 37.5°C [99.5°F] and as high as 39.7°C [103.5°F]) was recorded for 40 percent of patients. Abdominal tenderness was noted for about half of the patients but was always generalized; no point or rebound tenderness, abdominal distention or organomegaly was observed.

The median leukocyte count was 9,400 per μl and a count over 10,000 was recorded in 34 percent. Occult blood was found in the stools of 42 (71 percent) of 59 patients tested, including 17 patients who did not have grossly bloody stools. All eight children tested had occult blood in their stools, but only 30 of 51 adults tested had this finding ($P=.02$, Fisher's exact test). Of 71 patients whose stools were examined 60 (85 percent) had polymorphonuclear leukocytes present. Of 14 patients with fever who had blood cultures, *C jejuni* was found in one culture.

There were 18 patients (13 male, 5 female) among the most seriously ill who had sigmoidoscopies, usually because of grossly bloody stools or prolonged diarrhea. The rectal mucosa appeared abnormal in 17 of the 18 patients; the findings ranged from erythema and edema to those indistinguishable from acute ulcerative colitis. Rectal biopsy specimens obtained from eight patients all showed inflammation of the lamina propria, with increased numbers of polymorphonuclear leukocytes and mononuclear cells. Abnormalities of the mucous glands were seen in all biopsy specimens, ranging from flattening of the epithelium and depletion of mucous cells to destruction of glands with formation of crypt abscesses. One specimen showed mucosal ulceration.

Course of the illness. One patient was in the hospital for treatment of a malignancy when he had diarrhea; all the others became ill at home. The median hospital stay for the 20 patients who were admitted to hospital was five days (range 3 to 37 days).

Of the 70 patients for whom the duration of illness was assessed, 37 were not treated with antimicrobial agents because their symptoms were diminishing or absent when *Campylobacter* infection was diagnosed; 68 percent had illness lasting a week or less. The 37 untreated patients were ill from 1 to 20 days (median 5 days) and 11 percent had relapses; 33 treated patients were ill from 3 to 31 days (median 8 days) and 30 percent had relapses before treatment. Of the 33 treated patients, 29 received erythromycin. No relapses occurred after treatment with erythromycin, but stools were not recultured.

Discussion

In a laboratory-based investigation such as ours, the population studied is biased toward those considered by a physician to be ill enough to

have specimens taken for culture. This form of selection favors recognizing the more severe and chronic manifestations of infection. Despite this phenomenon, or perhaps as a result of it, during the two years of our study *Campylobacter* was more frequently isolated than *Salmonella* or *Shigella* from the stools of patients with diarrhea. The seasonality of *Campylobacter* infection in Denver resembled that seen in England and Belgium.[1] The slightly higher rate at which *Campylobacter* was identified in male patients perhaps reflects their more frequent exposure to infection. Although the initial studies of *Campylobacter* infection were done in children's hospitals,[1,4,10] our study shows it clearly affects adults also. The high rate of isolation of *Campylobacter* from young men during the summer months further emphasizes its importance in adults.

The symptoms of *Campylobacter* infection could not be differentiated easily from those of infection due to other bacterial or viral causes of acute gastroenteritis,[11] and the severity of illness varied greatly. The frequent findings of fever, blood in stools and fecal leukocytes were helpful because enterotoxigenic *Escherichia coli* and rotaviruses, which commonly cause diarrhea, are not associated with such findings, even in laboratory-based surveys.[11] Thus the presence of blood and neutrophils in the feces of a febrile patient strongly suggests an inflammatory bacterial process[11-14] such as that caused by *Campylobacter, Salmonella, Shigella, Yersinia* or *Clostridium difficile*.

Occasionally abdominal pain may be the primary symptom of *Campylobacter* as well as *Yersinia* and *Shigella* infections[11,13]; patients having laparotomy or appendectomy because of severe pain have been reported.[15] We observed no extra-intestinal complications of *Campylobacter* infection, though such complications as convulsions, meningitis and arthritis have been reported.[16-18] The finding that a subset of patients with severe illness had pathologic changes in the colon should be interpreted with caution. Changes seen in several other patients[19-21] suggest that the small intestine may be the primary target organ. Therefore, colonic involvement in more severe *Campylobacter* infections may represent a so-called spill-over phenomenon, sequential sites of attack or may relate to the vulnerable site for infection in that patient.[22,23]

In this review the patients who were ill longer and had suffered relapses were more likely to be treated with erythromycin. Only a prospective controlled clinical trial will determine the proper role of erythromycin or other agents in the treatment of *Campylobacter* enteritis. Until such data are available it seems prudent to give erythromycin to patients with persistent or severe enteritis due to *C jejuni*.

The 124 patients discussed in this report indicate the wide spectrum of gastrointestinal illness caused by *C jejuni*. *Campylobacter* infection may cause an illness that ranges from mild diarrhea to severe enteritis, or inflammation that mimics ulcerative colitis.[22,23] Because it is such a common enteric pathogen, *C jejuni* should be sought routinely in fecal specimens from patients with diarrhea.

REFERENCES

1. Butzler JP, Skirrow MB: Campylobacter enteritis. Clin Gastroenterol 1979 Sep; 8(3):737-765

2. Skirrow MB: Campylobacter enteritis: A "new" disease. Br Med J 1977 Jul 2; 2(6078):9-11

3. Steele TW, McDermott S: Campylobacter enteritis in South Australia. Med J Aust 1978 Oct 21; 2:404-406

4. Karmali MA, Fleming PC: Campylobacter enteritis in children. J Pediatr 1979 Apr; 94:527-533

5. Svedhem A, Kaijser B: *Campylobacter fetus* subspecies *jejuni*: A common cause of diarrhea in Sweden. J Infect Dis 1980 Sep; 142:353-357

6. Bokkenheuser VD, Richardson NJ, Bryner JH, et al: Detection of enteric campylobacteriosis in children. J Clin Microbiol 1979 Feb; 9:227-232

7. Blaser MJ, Glass RI, Huq MI, et al: Isolation of *Campylobacter fetus* subsp. *jejuni* from Bangladeshi children. J Clin Microbiol 1980 Dec; 12:744-747

8. Blaser MJ, Berkowitz ID, LaForce FM, et al: Campylobacter enteritis: Clinical and epidemiologic features. Ann Intern Med 1979 Aug; 91:179-185

9. Edwards PR, Ewing WH: Identification of Enterobacteriaceae, 3rd Ed. Minneapolis, Burgess Publishing, 1972

10. Pai CH, Sorger S, Lackman L, et al: Campylobacter gastroenteritis in children. J Pediatr 1979 Apr; 94:589-591

11. Plotkin GR, Kluge RM, Waldman RH: Gastroenteritis: Etiology, pathophysiology and clinical manifestations. Medicine 1979 Jan; 58:95-114

12. Harris JC, DuPont HL, Mornick RB: Fecal leukocytes in diarrheal illness. Ann Intern Med 1972 May; 76:697-703

13. Marks MI, Pai CH, Lafleur L, et al: *Yersinia enterocolitica* gastroenteritis: A prospective study of clinical, bacteriologic, and epidemiologic features. J Pediatr 1980 Jan; 96(1):26-31

14. Larson HE: Pseudomembranous colitis is an infection. J Infect Dis 1980 Sep; 1:221-226

15. Hay DJ, Ganguli LA: Campylobacter enteritis presenting as an acute abdomen. Postgrad Med J 1980 Mar; 56(653):205-206

16. Havalad S, Chapple MJ, Kahakachchi M, et al: Convulsions associated with campylobacter enteritis. Br Med J 1980 Apr; 280: 984-985

17. Norrby R, McCloskey RV, Zackrisson G, et al: Meningitis caused by *Campylobacter fetus* ssp *jejuni*. Br Med J 1980 May 10; 280(6224):1164

18. Kosunen TU, Kauranen O, Martio J, et al: Reactive arthritis after campylobacter jejuni enteritis in patients with HLA-B27 (Letter). Lancet 1980 Jun 14; 1(8181):1312-1313

19. King EO: The laboratory recognition of *Vibrio fetus* and a closely related vibrio isolated from cases of human vibriosis. Ann NY Acad Sci 1962 Oct; 98:700-711

20. Wheeler WE, Borchers J: Vibrionic enteritis in infants. Am J Dis Child 1961 Jan; 101:60-66

21. Cadranel S, Rodesch P, Butzler JP, et al: Enteritis due to "related vibrio" in children. Am J Dis Child 1973 Aug; 126: 152-155

22. Lambert ME, Schofield PF, Ironside AG, et al: Campylobacter colitis. Br Med J 1979 Mar 31; 1(6167):857-859

23. Blaser MJ, Parsons RB, Wang W-LL: Acute colitis caused by *Campylobacter fetus* ssp *jejuni*. Gastroenterology 1980 Mar; 78:448-453

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Carcinoma of the Lung in Nonsmoking Chinese Women

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The records of 452 lung cancer patients seen in San Francisco between 1972 and 1979 were retrospectively analyzed according to race, sex, findings at histology and smoking history. Of 31 Chinese women with adenocarcinoma or large cell undifferentiated carcinoma, 20 (64.5 percent) had never smoked, which is in sharp contrast to all other subsets. At least 12 of the women were of Cantonese origin. These data support the findings of previous studies carried out in Cantonese women residing in Hong Kong, Singapore and Hawaii. As the incidence of adenocarcinoma in nonsmokers is appreciably higher than that noted in Canton, the possibility must be considered that the cause may be the result of an interaction between some traditional and nontraditional exposures.

IN A RECENT REVIEW of lung cancer patients seen in the Department of Radiation Therapy, St. Francis Memorial Hospital, San Francisco, an interesting subset was identified, namely, nonsmoking Chinese women with either adenocarcinoma or large cell undifferentiated carcinoma. The purpose of this report is to carefully analyze this group and compare the findings with those of previous studies.

Patients and Methods

From 1972 through 1979 approximately 2,500 new patients with cancer were seen in the Department of Radiation Therapy, including 452 with lung carcinoma. Through the services of the hospital's cancer registry, the pertinent clinical data were extracted from the patients' records, computerized and then analyzed accordingly. All histocytopathology was reviewed at the time of diagnosis by a St. Francis Hospital staff pathologist. The material was variable depending on the types of diagnostic procedures carried out.

St. Francis Memorial Hospital is situated near San Francisco's Chinatown and therefore a relatively large number of Chinese patients are referred there for radiation therapy. Approximately 14 percent of the department's total patient population were Chinese, compared with 26 percent of the lung cancer patients. The remainder were predominantly white. In the lung cancer group, there were overall 294 men and 158 women; the male-to-female ratios were 73 to 43 (1.7:1) Chinese and 221 to 115 (1.9:1) non-Chinese. Of the 116 Chinese patients 99 (85 percent) were born in China.

Results

Adenocarcinoma

The percentage of lung cancer patients with adenocarcinoma was Chinese, 24 percent, and non-Chinese, 14 percent. Of the 73 Chinese male patients, 11 (15.1 percent) had adenocarcinoma; of the 43 Chinese female patients, 17 (39.5 percent) had adenocarcinoma. The 17 Chinese fe-

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male patients with adenocarcinoma were all born in China; six were from Canton, one from Hong Kong, one from Hangchow and nine were not further specified. Their ages ranged from 29 to 86, with an average of 68 years. Duration of stay in the United States was recorded in nine women and ranged from 1 to 61 years. Occupations included the following: housewife, 10; seamstress, 4; data processor, 1; not specified, 2. Of the 17 women, 12 (71 percent) had never smoked. Of the remainder, two women smoked fewer than ten cigarettes a day and two women smoked between two and three packs per day. The specific smoking history in one female smoker was unknown.

Large Cell Undifferentiated Carcinoma

The percentage of large cell undifferentiated carcinoma was essentially the same in the Chinese (23 percent) and non-Chinese (24 percent) populations. This diagnosis was made in 18 percent of Chinese men and 32 percent of Chinese women. Of the 14 Chinese women with this diagnosis, 11 were born in China: 6 were from Canton, 1 was from Hong Kong and area of origin was not further specified in 4. Three were born in California. Their ages ranged from 29 to 80, with an average of 61.5 years. Occupations included the following: housewife, 4; seamstress, 3; baker, 1; bakery clerk, 1; waitress, 1; grocery clerk, 1; not specified, 3. The eight (57 percent) nonsmokers were all born in China. Of the six smokers, two smoked less than a pack, three smoked a pack and one smoked one to two packs of cigarettes per day.

Histocytologic Distribution

Table 1 shows the histocytologic distribution according to race and sex. In the present series, 17 and 14 of the 43 Chinese women (that is, 72.1 percent) had adenocarcinoma and large cell undifferentiated carcinoma, respectively. Of these 31 patients 28 were born in China and 20 (64.5 percent) were nonsmokers. This is contrasted with a negative smoking history in two of nine (22.2 percent) Chinese women having squamous cell or small cell undifferentiated carcinoma, 12 percent of Chinese men, 5 percent of non-Chinese men

TABLE 1.—*Histocytologic Distribution of 452 Cases of Lung Cancer by Sex and Race*

	Chinese				*Non-Chinese*			
	Male		*Female*		*Male*		*Female*	
Findings of Histocytology	*No.*	*Percent*	*No.*	*Percent*	*No.*	*Percent*	*No.*	*Percent*
Total	73	100.0	43	100.0	221	100.0	115	100.0
Adenocarcinoma	11	15.1	17	39.5	28	12.7	20	17.4
Large cell undifferentiated	13	17.8	14	32.6	51	23.1	31	27.0
Squamous cell carcinoma	30	41.1	8	18.6	76	34.4	25	21.7
Small cell or oat cell carcinoma	14	19.2	1	2.3	46	20.8	28	24.3
Carcinoma, other	..	...	1	2.3	2	.9	5	4.3
Carcinoma, not otherwise specified	2	2.7	..	...	8	3.6	1	.9
No histology or cytology done	3	4.1	2	4.7	10	4.5	5	4.3

TABLE 2.—*Smoking History of Lung Cancer Patients by Histocytology, Sex and Race*

		Chinese				*Non-Chinese*			
Findings of Histocytology	*Sex*	*Total Number*	*Smoker*	*Non-smoker*	*Unknown*	*Total Number*	*Smoker*	*Non-smoker*	*Unknown*
			Percent Distribution				*Percent Distribution*		
Adenocarcinoma	♂	11	72.8	18.2	9.0	28	96.4	...	3.6
	♀	17	17.6	70.6	11.8	20	85.0	10.0	5.0
Large cell	♂	13	76.9	15.4	7.7	51	96.0	2.0	2.0
	♀	14	42.9	57.1	..	31	83.9	6.4	9.7
Squamous cell	♂	30	93.4	3.3	3.3	76	98.7	1.3	..
	♀	8	75.0	25.0	..	25	88.0	4.0	8.0
Small cell or oat cell	♂	14	92.9	..	7.1	46	95.7	...	4.3
	♀	1	100.0	..	..	28	92.8	3.6	3.6
Carcinoma, other	♂	..	...	..	..	2	100.0	...	..
	♀	1	100.0	..	..	5	80.0	20.0	..
Carcinoma, not otherwise specified	♂	2	100.0	..	..	8	62.5	25.0	12.5
	♀	..	...	..	..	1	...	100.0	..
No histology or cytology done	♂	3	100.0	..	..	10	90.0	...	10.0
	♀	2	50.0	50.0	..	5	80.0	20.0	..

and 14 percent of non-Chinese women (Table 2).

Among the four sex/race groups, the percentage of nonsmoking Chinese women was significantly higher (P less than .0001) than any other sex/race group. These nonsmoking Chinese women were mostly concentrated in the adenocarcinoma and the large cell undifferentiated carcinoma groups. Interestingly, among Chinese female patients in other histocytologic groups, the percentage with a negative smoking history was higher than other sex/race groups but not as high as those with adenocarcinoma or large cell undifferentiated carcinoma.

It is estimated that approximately 85 percent of the San Francisco Chinese originate from Canton. Of our 28 China-born nonsmoking women, 14 had recorded their birthplace as Canton or Hong Kong, 1 (3.6 percent) as Hangchow and the remaining 13 (46.4 percent) not otherwise specified. The presumption that most of the unspecified are of Cantonese origin seems reasonable.

Discussion

The frequency of occurrence of adenocarcinoma in Chinese women is well recognized but there have been few studies of smoking history or other possible carcinogenic exposure, and only one such study in US-residing Chinese (Hawaii).[1]

United States

Fraumeni and Mason[2] studied cancer mortality among Chinese Americans from 1950 through 1969 by using death certificates. They were unable to sort out foreign-born from American-born Chinese. Death patterns of 1,139 Chinese females were compared with those of whites and blacks. A significant excess of lung cancer mortality in Chinese women was noted, with no change over time.

Hinds and colleagues[1] compared lung cancer risk associated with smoking in Japanese, Chinese and Hawaiian women. They noted the association to be least for Chinese women, with only squamous cell and small cell carcinoma significantly related to smoking. Reference was not made to the patient's place of birth.

Hong Kong

Lee and Ts'O[3] in 1963 noted that adenocarcinoma is the most common type of lung cancer in Hong Kong Chinese, occurring in 47 percent of women with lung cancer and 36 percent of men with lung cancer. Chan and MacLennan,[4] in a more recent review of Hong Kong Chinese, observed that incidence of adenocarcinoma in women was 34 percent, compared with 16 percent in men. There was equal incidence of large cell undifferentiated carcinoma (that is, 16 percent) for each sex.

Chan and co-workers[5] carried out an in-depth epidemiologic analysis of 397 Hong Kong patients with bronchial cancer (208 men and 189 women) using a control group of orthopedic patients in the same general age group. For the cancer group, the nonsmoking distribution was women, 44 percent, and men, 21 percent. Of the 189 women, 88 percent were of Cantonese origin. Adenocarcinoma was noted in 34 percent of the women and 22 percent of the men. There were also four women with large cell undifferentiated carcinoma. In this total of 68 women, half were nonsmokers, as compared with a 30-percent nonsmoker incidence in the women with squamous cell or small cell undifferentiated carcinomas. Of the potentially correlative factors studied, including socioeconomic status, air pollution, occupation and kerosene stove cooking, none were rewarding.

Singapore

Shanmugaratnam,[6] using the Singapore Cancer Registry, reviewed 1,072 new cases of lung cancer seen in the city from 1968 through 1970. For this form of cancer, now the most common one in Singapore, there was an age-standardized incidence in women of 14.9, among the highest recorded for women in any country. Singapore is a city of 2.1 million population, 76 percent being Chinese. In 1966 immigrants made up 56 percent of the population aged 30 through 59 years and 82 percent of those aged 60 and over. The Chinese in Singapore mostly originate from the southeastern provinces of Fukien and Canton. The major dialect groups in Singapore are Hokkien (42.2 percent of the Chinese population) derived from Fukien, Teochew (22.4 percent) from the Teochew district of Canton (on the Fukien border) and Cantonese (17.0 percent) who originate from other parts of Canton. These data were confirmed by Law and co-workers,[7] who analyzed 1,747 cases of lung cancer entered into the Singapore Cancer Registry from 1968 through 1972.

MacLennan and associates,[8] further analyzing the Singapore Cancer Registry data of 1968 through 1970, noted the annual incidence of lung cancer in Cantonese women was 25.6, compared with 12.8 in the Hokkien and 10.2 in the Teochew,

with no comparable difference among Chinese men. The relative risks of smoking and other factors from 1972 to 1973 were studied, using matched hospital patients as controls. Virtually all male patients and 90 percent of controls were smokers. In the women, approximately half the Cantonese patients and controls were smokers. In Cantonese women, the percentages of patients with a positive smoking history according to histology were as follows: small cell carcinoma 85.7 percent, epidermoid 80 percent, large cell 66.7 percent and adenocarcinoma 31.3 percent. Other factors studied and discounted included occupational exposure, incense and mosquito coils, cooking, opium, diet and socioeconomic status.

According to these authors, there has been a recent rise in the incidence of lung cancer in Cantonese women in Singapore and Hong Kong but not in Canton. This justifiably suggests that a search be carried out for nontraditional exposures, without precluding the possibility that such exposure might interact with some traditional exposure.

Summary

This San Francisco-based study points out the relatively high percentage of nonsmoking Chinese women with adenocarcinoma and large cell undifferentiated carcinoma of the lung. Combining these two subsets, there are 31 women, of whom 20 (64.5 percent) have never smoked. Of these, 28 (90.3 percent) were born in China and at least 12 (43 percent) of these patients were of Cantonese origin. There were no differences found with regards to age, stage of disease, place of birth in China or other characteristics that could account for the variation between the Chinese female nonsmokers and smokers in the adenocarcinoma and large cell undifferentiated carcinoma groups. It is concluded that Chinese women, specifically those of Cantonese origin, in San Francisco and elsewhere are exposed to a potent lung carcinogen other than tobacco that may interreact with some traditional exposure to increase their susceptibility to adenocarcinoma and large cell undifferentiated carcinoma of the lung.

REFERENCES

1. Hinds MW, Stemmermann GN, Yang HY, et al: Differences in lung cancer risk from smoking among Japanese, Chinese and Hawaiian women in Hawaii. Int J Cancer 1981; 27(3):297-302

2. Fraumeni JF Jr, Mason TJ: Cancer mortality among Chinese Americans, 1950-69. J Natl Cancer Inst 1974 Mar; 52:659-665

3. Lee SH, Ts'O TOT: Histological typing of lung cancer in Hong Kong. Br J Cancer 1963 Mar; 17:37-40

4. Chan WC, MacLennan R: Lung cancer in Hong Kong Chinese: Mortality and histological types, 1960-1972. Br J Cancer 1977 Feb; 35(2):226-231

5. Chan WC, Colbourne MJ, Fung SC, et al: Bronchial cancer in Hong Kong 1976-1977. Br J Cancer 1979 Feb; 39:182-192

6. Shanmugaratnam K: Epidemiological studies of lung cancer in Singapore, *In* Hirayama T (Ed): Cancer in Asia. Baltimore, University Park Press, 1976, pp 153-158

7. Law CH, Day NE, Shanmugaratnam K: Incidence rates of specific histological types of lung cancer in Singapore Chinese dialect groups, and their aetiological signifificance. Int J Cancer 1976 Mar 15; 17(3):304-309

8. MacLennan R, Da Costa J, Day NE, et al: Risk factors for lung cancer in Singapore Chinese, a population with high female incidence rates. Int J Cancer 1977 Dec 15; 20(6):854-860

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Medical Progress

Do Coronary Artery Bypass Operations Prolong Life?

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Coronary artery bypass operations improve survival in patients with symptomatic left main coronary artery stenosis, but whether or not longevity is improved in other patients has been controversial. Small clinical studies, even when randomized, have not sufficiently controlled for the heterogeneous distribution of risk factors in patient cohorts treated medically and surgically. The first randomized study large enough to overcome such problems, the Veterans Administration Cooperative Study, showed that coronary artery bypass procedures prolonged survival only in the high-risk subgroup. The surgically treated patients suffered more perioperative morbidity and mortality and had worse long-term survival than similar patients operated on in more recent years. The European Coronary Surgery Study Group recently reported that the three-year to five-year survival of symptomatic patients with triple-vessel disease and normal left ventricular function was better if patients were randomly assigned to surgical therapy. The third and by far the largest randomized study, the Coronary Artery Surgery Study (CASS), has not yet reported long-term follow-up results.

Large clinical studies, both randomized and nonrandomized, that have subgrouped patients by the number of diseased coronary arteries and by the degree of left ventricular dysfunction all show that survival with single-vessel disease is excellent and not improved by operation. Medically treated patients with double- and triple-vessel disease who have good left ventricular function generally now have a five-year survival greater than 85 percent and only two of the major studies suggest that it is improved by operation. The results of most studies, however, suggest that bypass operation prolongs survival in symptomatic patients when left ventricular dysfunction coexists with double- and triple-vessel disease. Continually improving surgical techniques may potentiate the small survival differences that are now apparent, but until then, because the survival differences are so small, it is recommended that limiting anginal symptoms remain the primary indication for a coronary bypass procedure for an individual patient.

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ABBREVIATIONS USED IN TEXT

CASS = Coronary Artery Surgery Study
ECSSG = European Coronary Surgery Study Group
LAD = left anterior descending
NYHA = New York Heart Association

THE CORONARY BYPASS PROCEDURE is now over 14 years old and is done on an estimated 110,000 Americans a year at an annual cost of $1.6 billion.[1-4] It is definitely effective in alleviating anginal symptoms, lessening the need for antianginal medications[5-8] and substantially prolonging the life of patients with symptomatic left main coronary artery disease.[7-9] Whether or not it prolongs the life of patients with stable angina without left main coronary artery disease is the controversial subject of this review.

Study of this question has been complicated by several factors. First, a "steady state" has not yet existed long enough to allow meaningful follow-up data to accumulate. The effectiveness of both medical and surgical therapy has improved considerably since the late 1960's, but probably at different rates and to different degrees.[8,10-15] Even now, the effectiveness of surgical therapy is very dependent on the surgeon and the perioperative care.[16] Second, there is the problem in randomized studies of patients "crossing over" from medical therapy to surgical therapy because surgical therapy is so effective in relieving angina when antianginal medications fail.[7,8,17] Third, the heterogeneity of coronary artery disease was not fully appreciated until recently. In most studies the variables that could affect survival were not initially defined and then not rigorously controlled for, so that small differences in baseline variables were just as likely to explain survival differences as whether the patients were treated medically or surgically. Fourth, differences in survival between surgically or medically treated patients over five-year periods are small, if present at all, so that large numbers of patients are needed to be able to statistically show that the differences are more likely to be due to the therapy than chance alone.

Predictors of Survival in Patients With Coronary Artery Disease

If the issue of survival of patients with coronary artery disease is to be intelligently addressed, it is first necessary to determine what baseline variables affect survival before any effect of a therapeutic intervention can be studied.[18-22] Too many studies in the early 1970's were based on the erroneous assumption that the only variable worth defining was the number of major coronary arteries stenosed. This assumption was largely due to reports from the Cleveland Clinic about long-term survival data on a cohort of 601 medically treated patients who underwent coronary angiography between 1963 and 1965.[23] After ten years of follow-up survival curves were published that implied that the number of major coronaries stenosed was highly predictive of prognosis.[24] But they also implied that the prognosis of patients with double- and triple-vessel disease was terrible, with 7 percent and 12 percent annual mortality respectively. Later studies of medically treated patients, most notably the Veterans Administration Cooperative Study,[17] showed that the survival of patients with multivessel disease was not nearly so bad as implied by the Cleveland Clinic data.[24] One explanation offered for the discrepancy was that wide use of propranolol hydrochloride and isosorbide dinitrate in the 1970's and more sophisticated coronary care techniques had significantly improved survival of medically treated patients. A more likely explanation is that a large proportion of the Cleveland Clinic patients had abnormal left ventricular function. Less than 40 percent of the patients with double- and triple-vessel disease had normal left ventricular contraction.[24,25] The investigators did show that subsequent survival was related to whether the left ventriculogram was normal, showed a localized wall motion abnormality, diffuse hypokinesis or an aneurysm, but did not factor this into the relation between the number of diseased coronaries and survival.[25]

Gross and co-workers[26] observed the survival rates of 231 medically treated patients with coronary artery disease who underwent angiography at the Montefiore Hospital between 1971 and 1974. They found that both the number of diseased coronaries and the left ventricular function affected survival but that left ventricular function was a much more important factor. Between 1966 and 1975, there were 153 medically treated patients studied at the Mayo Clinic and similar conclusions were drawn.[27] There was an apparent correlation between survival rate and coronary artery anatomy but there was an even more dramatic correlation with the ejection fraction. The authors noticed that the proportion of patients with poor left ventricular function increased with increasing severity of coronary artery disease and concluded that this explained the apparent corre-

lation between coronary artery anatomy and survival. If the ejection fraction was normal (greater than 50 percent), even patients with triple-vessel disease had a 90 percent three-year survival. An ongoing study of asymptomatic and mildly symptomatic patients with coronary disease, 75 percent of whom have ejection fractions greater than 50 percent, has shown an annual mortality of only 2 percent in medically treated patients with double- and triple-vessel disease.[28] The Veterans Administration Cooperative Study reported a 1 percent annual mortality for patients with multivessel disease and normal left ventricular function.[29] The European Coronary Surgery Study Group (ECSSG) reported a 2.8 percent annual mortality for a similar group of patients.[7]

TABLE 1.—*Independent Variables Significantly Predictive of Survival of Medically and Surgically Treated Patients**

Cohort	*Step†*	*Variable Entered*	x^2_i
Medical (N=50)			*Percent*
	1	Ejection fraction	48.54
	2	Age	17.16
	3	Number of vessels with stenosis(es) ≥70%	7.36
	4	Ventricular arrhythmia	4.46
Surgical (N=913)			
	1	Ventricular arrhythmia	19.40
	2	Ejection fraction	13.22
	3	Heart murmur	10.96
	4	Left main coronary artery stenosis	7.94
	5	Use of diuretics	5.38

N=number of patients used in each Cox's regression analysis.

*From Hammermeister and co-workers[18] and the Seattle Heart Watch

†Cox's regression analysis was used for stepwise selection of covariates.

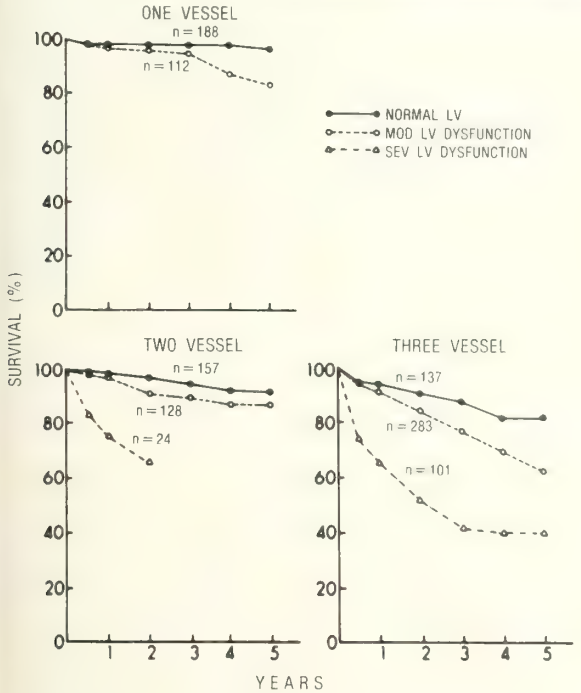

Figure 1.—Harris et al[19] showed that both left ventricular function and extent of coronary artery disease were predictive of survival at the $P<.01$ level. LV=left ventricle, MOD=moderate, SEV=severe. (Reproduced with the permission of Robert Rosati, MD, and the American Heart Association, Inc.)

Multivariate Analysis of Survival

In the past three years, two large studies from Seattle[18] and Duke University[19] have been reported that used multivariate analysis to define multiple independent baseline variables predictive of subsequent survival. Independent variables relating to left ventricular function were the most predictive of survival in both studies. The study by Hammermeister and associates[18] used 2,616 patients observed in the Seattle Heart Watch, a nonrandomized registry of most of the patients who

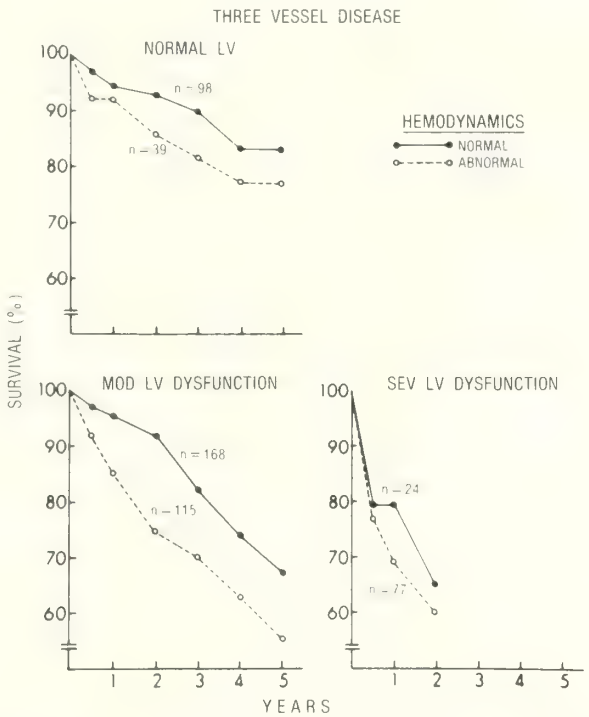

Figure 2.—Cumulative survival rates of medically treated patients with triple-vessel disease were related to both left ventricular contraction pattern and abnormal hemodynamic measures (arteriovenous oxygen difference >5 ml per dl or left ventricular end-diastolic pressure >17 mm of mercury). MOD=moderate, SEV=severe. (Reproduced with the permission of Robert Rosati, MD, and the American Heart Association, Inc.[19])

had coronary arteriography in the Seattle area between 1969 and 1974. For medically treated patients, ejection fraction was the best predictor of survival, followed in importance by age, number of diseased coronary arteries and ventricular arrhythmias (Table 1). The study by Harris and colleagues[19] used 1,214 patients from the Duke University Computer Registry, a registry of all the patients who have had cardiac catheterization at Duke since 1969, and found that the following factors were predictive of subsequent survival at the $P<.01$ level: left ventricular function, number of diseased coronary arteries, New York Heart Association (NYHA) class IV heart failure, arteriovenous oxygen difference, left ventricular end-diastolic pressure, anterior left ventricular asynergy, nonspecific intraventricular conduction defect (probably because it is associated with ischemic cardiomyopathies), history of peripheral vascular disease, premature ventricular contractions on the resting electrocardiogram and, of course, left main coronary artery stenosis. Progressive chest pain, nocturnal chest pain and left bundle branch block were significant predictors of survival at the $P<.05$ level. For example, the two most important predictors of survival, left ventricular function and the extent of coronary artery disease, interacted as shown in Figure 1. However, the prediction of survival of patients characterized as having triple-vessel disease with either normal, moderately abnormal or a severely abnormal contraction pattern on the left ventriculogram could be further enhanced by defining whether normal or abnormal hemodynamic measures (that is, arteriovenous oxygen difference and left ventricular end-diastolic pressure) were present (Figure 2). Progressive chest pain was the most important independent clinical variable reflecting ischemia. Not all of the patients with progressive chest pain were considered to have unstable angina necessitating admission to a coronary care unit, but the progressive pattern of angina pectoris was still consistently associated with a decreased survival across all degrees of coronary disease and ventricular function (Figure 3).[19]

In the surgical cohort of the Seattle Heart Watch, predictors of survival in order of importance were ventricular arrhythmias, ejection frac-

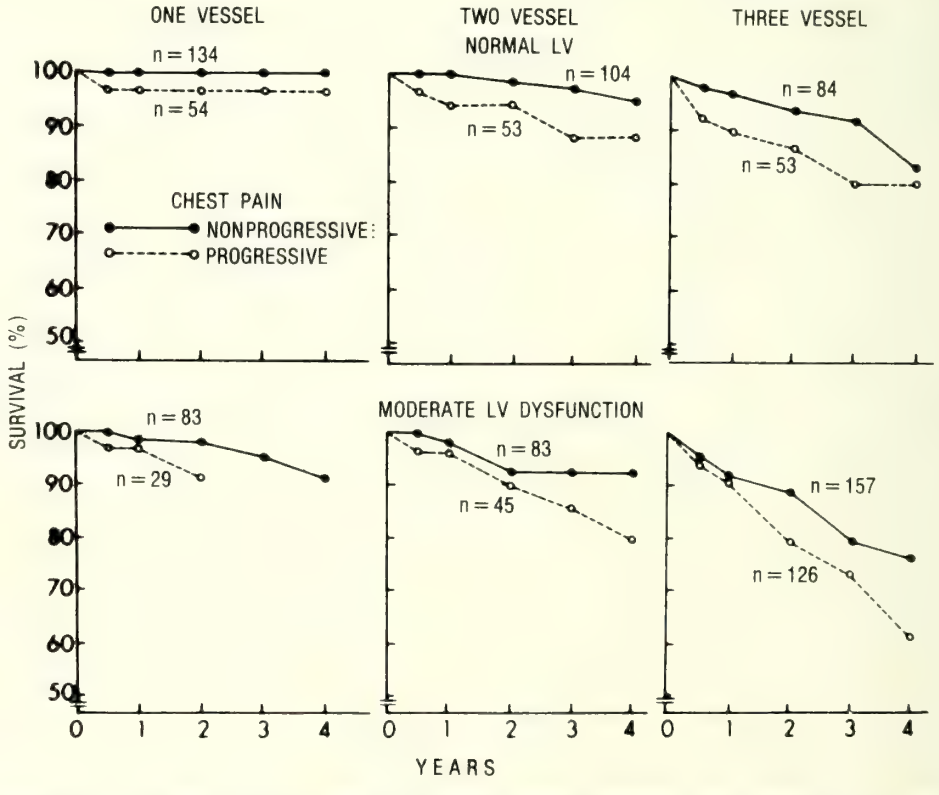

Figure 3.—Cumulative survival rates of medically treated patients were related to progressive chest pain ($P<.05$), extent of coronary artery disease ($P<.01$) and left ventricular (LV) function ($P<.01$). Reproduced with the permission of Robert Rosati, MD, and the American Heart Association, Inc.[19])

tion, heart murmur (probably reflecting ischemic papillary muscle dysfunction), left main coronary artery disease and diuretic use (Table 1).[18] Notably absent as a significant variable was the number of diseased coronary arteries, a factor presumably altered by the coronary bypass procedure. This phenomenon was also seen in the surgical cohort of the VA Cooperative Study.[30]

In both the medical and surgical cohorts reported by Hammermeister and associates,[18] there was more than an 18-fold difference in survival between the subgroup with none of the independently significant risk factors and the subgroup with all of them. It should be readily seen how slight differences in the distribution of risk factors between two groups being compared could lead to differences in survival that might be attributed to the treatment unless comparability was rigorously assured. For example, in 1974 McNeer and co-workers[31] reported that a high-risk subgroup of the Duke University Computer Registry cohort with triple-vessel disease and abnormal left ventricular function had a significantly better survival with surgical therapy than with medical therapy. But when the authors analyzed these data two years later they found that the difference was just as likely to have been related to distributional differences in risk factors as to the treatment.[32]

Even randomization does not guarantee comparability. Lee and colleagues[20] simulated a randomized trial using 1,073 medically treated patients in the Duke University Computer Registry. Patients were blocked into groups of similar age and number of diseased vessels, then randomized. Baseline characteristics previously shown to be predictive of survival were not significantly different when compared by univariate analysis. In a subgroup with impaired left ventricular function and triple-vessel disease, survival was significantly better in one group ($P<.025$) even though the only intervention was randomization. The distribution of baseline variables in this subgroup also was not significantly different when compared by univariate analysis. Only when multivariate analysis was used could it be shown that the difference in survival was better explained by subtle differences in important baseline variables than by the "intervention."

Thus, when statistical differences are noted in subgroups of patients with coronary artery disease, care must be used to rigorously assure comparability, perhaps by multivariate analysis. Even then, significant differences can be seen that are due to chance alone if comparisons of multiple subgroups are made. For example, if ten nonoverlapping subgroups were compared, there would be a 40 percent chance that at least one significant result ($P<.05$) would be observed, even if the treatment were ineffective.[20]

Randomized Prospective Clinical Trials

Prospective randomization of patients into treatment groups of sufficient size is considered the best way to get initial comparability of the groups to be studied.[33] Only three prospective randomized clinical trials have used sufficiently large sample sizes. The Coronary Artery Surgery Study (CASS) randomly assigned 780 patients between 1975 and 1979 but no long-term follow-up results have been reported yet.[16,34-38] The second largest trial, the ECSSG, recently reported its five-year cumulative mean follow-up results.[7] The third, the Veterans Administration Cooperative Study, is the oldest of the three and definitely the most controversial of all the studies on this subject.[6,9,17,29,30,39-42] Because the latter study is so controversial and because the results of other studies are always contrasted with the VA Cooperative Study results, it will be discussed first.

The VA Cooperative Study

Between 1970 and 1974 there were 13 VA hospitals that enrolled patients, but only the data from the last two years were published because the operative mortality was excessively high in the first two years.[30] Even in the last two years of the study, 3 of the 13 cooperating VA hospitals reported a 23 percent operative mortality, while the other 10 reported a 3.4 percent operative mortality.[42,43] Only patients with stable angina without a recent myocardial infarction were included. After subgrouping the patients with left main coronary artery stenosis, 310 patients were randomly assigned to medical therapy and 286 patients were randomly assigned to surgical therapy.[17]

At six years of cumulative mean follow-up, the survival of the entire medical cohort was 76 percent and that of the surgical cohort was 79 percent (not significantly different) (Figure 4).[39] In the subgroup with the left main coronary disease, the survival of the surgically treated patients was significantly better than the medically treated patients ($P<.001$, Figure 5).[9,30,41] A subgroup classified as high risk on the basis of clinical variables had a significantly better survival if

treated surgically rather than medically ($P<.01$).[42] Those in the low- and medium-risk subgroups had no survival advantage if treated surgically.

This study has been criticized for using stringent inclusion and exclusion criteria that resulted in a very select, albeit well-defined population.[14,15,44,45] The criteria excluded patients with unstable angina or recent myocardial infarction, a population that frequently has bypass surgical procedures today.

Of the surgical group, 6 percent refused operation but 17 percent of the medical group eventually had bypass procedures.[17] It could be argued that the patients who refused operation were probably minimally symptomatic and therefore low-risk patients, while the medical to surgical crossovers were more symptomatic and therefore higher risk patients, thus biasing the results away from surgical therapy. A study by Pryor and associates[46] suggested the opposite. They analyzed the risk factors of the patients in the Duke University Computer Registry and found that the patients who crossed over from medical to surgical therapy actually had fewer risk factors that could adversely affect survival than those who did not cross over. Nonetheless, the three-year survival results of the VA Cooperative Study were the same whether the crossover patients were left in their original groups, placed in the group to which they crossed over or eliminated from the analysis altogether.[17]

The short-term surgical results reflecting operative technique and perioperative care, perioperative mortality, perioperative infarctional rate and graft patency rate have justifiably been the most criticized aspects of the study. The rates were comparable with those of other studies published during the same time period,[30] but they are much worse than some from the same period that were

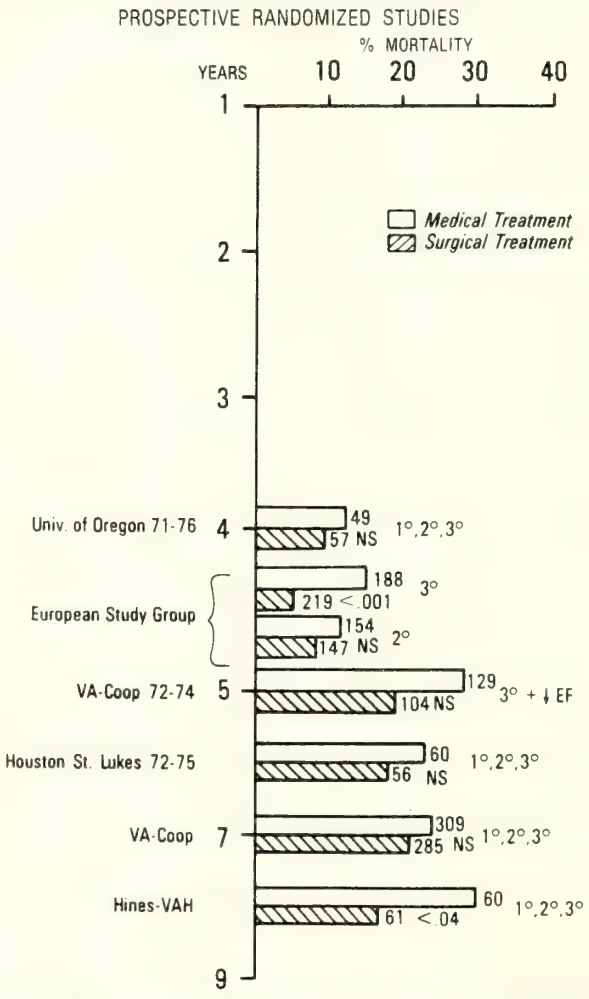

Figure 4.—Composite graph of medical and surgical cumulative mortality from prospective randomized studies. The numbers above the bars indicate the number of patients in each cohort or subgroup and significant differences between the medical and surgical groups, if any. 1° = single-vessel disease, 2° = double-vessel disease, 3° = triple-vessel disease, ↓EF = decreased ejection fraction, NS = not significant. (From European Study Group,[7] University of Oregon,[62] VA Cooperative,[9,39] Houston-St. Lukes,[61] Hines-VAH.[39,60])

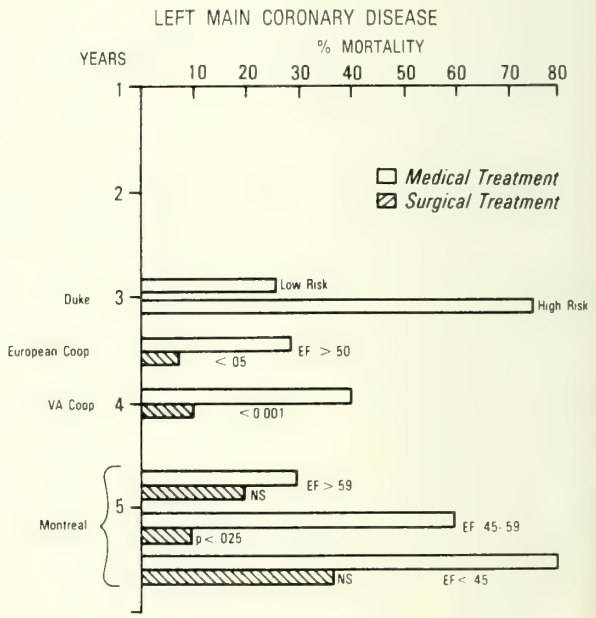

Figure 5.—Composite graph of mortality data for patients with left main coronary artery disease from two large randomized studies and two nonrandomized studies. The notations above the bars refer to the type of subgroup of patients with left main disease and the significance, if any, between the comparable surgically and medically treated patients. (EF = ejection fraction, NS = not significant.) (From Duke,[74] European Co-op,[7] VA Co-op[9] and Montreal.[73])

later published[13,47-52] and most of the recently published rates for operative mortality, infarction and graft patency. Specifically, the perioperative (30-day) mortality in the VA Cooperative Study was 5.6 percent, while perioperative mortality from 0.4 percent to 2 percent is closer to the norm in more recent reports.* The perioperative infarctional rate (development of a new Q wave on the electrocardiogram) was 18 percent, while the current standard at major medical centers is about 5 percent.[15,44,49,50,53-55] The graft patency rate at one year was 69 percent, while most centers report patency rates from 80 percent to 90 percent.[15,49,50,52,54-59] Thus, in the sense that the short-term results reflecting operative technique and perioperative care in the VA Cooperative Study do not compare with those being achieved today in major medical centers, the results of the VA Cooperative Study are already obsolete.

The European Study Group Trial

The ECSSG recently published five-year cumulative mean follow-up results of their prospective randomized cooperative study of stable angina in patients with multivessel disease and an ejection fraction greater than 50 percent[7] (Figure 4). In this trial 373 patients were randomly assigned to receive medical therapy and 395 to receive surgical therapy between 1973 and 1976. The operative mortality was 3.5 percent. After five years of cumulative mean follow-up, the survival of patients with triple-vessel disease randomly assigned to surgical therapy was 95 percent, but only 85 percent if randomly assigned to medical therapy ($P<.001$). The 92 percent survival of patients with double-vessel disease randomly assigned to surgical therapy was not significantly better than the 87.5 percent survival of patients randomly assigned to medical therapy.

Other Randomized Prospective Clinical Trials

CASS is a cooperative trial involving 11 medical centers in the United States and Canada that prospectively randomized 780 patients between 1975 and 1979.[16,34-38] Long-term survival results have not yet been published. The only two other randomized prospective trials were too small to be conclusive.

The Houston St. Luke's Episcopal-VA hospitals study was the first randomized one to be reported.[60] At last report 60 medical patients and 56 surgical patients had been followed for a cumulative mean of 66 months.[61] The 23 percent medical mortality and 18 percent surgical mortality were not significantly different (Figure 4).

Kloster and co-workers[52] reported on a randomized trial of 106 patients at the University of Oregon. There was no difference in the four-year survival (Figure 4), but they found that the five-year probability of unstable angina developing was 51 percent in the medical group and only 34 percent in the surgical group.[62]

Nonrandomized Studies of Concurrent and Matched Cohorts

There are only a few nonrandomized studies in which concurrent and matched controls were used. Vismara and colleagues[56] observed 217 nonrandomized patients with multivessel disease who had cardiac catheterization at the Sacramento Medical Center between 1970 and 1973. At 39 months of mean follow-up, there was a significantly greater incidence of so-called sudden cardiac death (death within six hours of the onset of symptoms) ($P<.001$) in the medically treated group (24 percent) than in the surgically treated group (6 percent), but the significance of the total mortality difference (35 percent vesus 16 percent) was not tested (Figure 6).

Vlietstra and co-workers[27] reported three-year survival data on 183 medically treated patients and 520 surgically treated patients who had cardiac catheterization at the Mayo Clinic between 1966 and 1972. There was more congestive heart failure in the medical group (11 percent versus 6 percent, $P<.01$) and more left main coronary disease in the surgical group (11 percent versus 5 percent, $P<.01$). Both the medically treated and surgically treated groups had a greater than 90-percent three-year survival when the ejection fraction was greater than 50 percent, even when triple-vessel disease was present. In the subgroup with moderately impaired ejection fractions between 25 percent and 49 percent, there was a significantly better survival in the surgical group (89 percent versus 68 percent, $P<.05$) (Figure 6).

The Seattle Heart Watch is a nonrandomized registry of most of the patients who had coronary angiography in the Seattle area between 1969 and 1974. Hammermeister and associates[63,64] observed 1,180 surgically treated patients and 350 medically treated patients for a cumulative mean of six years. Therapy was not randomly assigned, so they dealt with that problem in three

*References 13, 16, 36, 45, 47, 49, 52-56.

ways. First, they divided the patients into eight subgroups by the number of major coronaries stenosed and the ejection fraction (Figure 7). All the subgroups with double-vessel disease and the subgroup with triple-vessel disease and an ejection fraction of 31 percent to 50 percent had significantly better survival with surgical therapy than with medical therapy.[64]

The second way they dealt with the nonrandomized data was by analysis of pairs.[21,64] One medically treated patient was paired to one or more surgically treated patients matched for each of seven independent variables previously shown by multivariate analysis to be predictive of survival (Table 1).[18] The patients with double-vessel disease again showed better survival with surgical therapy at five years of cumulative mean follow-up ($P < .0002$).[21,64] In patients with triple-vessel disease overall survival was not different ($P = .42$).

The third method used multivariate analysis to determine whether surgical as opposed to medical therapy was a significant factor in favorably affecting survival.[22] The subsets that had significantly better survival with surgical therapy were those with multivessel disease, an ejection fraction greater than 30 percent, age greater than 48, NYHA functional classes I and II and those without heart murmurs, diuretic use, congestive heart failure, cardiomegaly or ventricular arrhythmias. They speculated that the subsets with left main coronary disease and those with an ejection fraction less than 31 percent did not show significant survival differences due to the small number of patients in those subsets. The surprising results of this analysis were that older patients and less symptomatic (NYHA classes I and II) patients seemed to benefit more from surgical therapy than their counterparts did from medical therapy. It is common practice to more readily recommend bypass procedure for younger and more symptomatic patients.

The high-risk subgroup from the Duke University Computer Registry with triple-vessel disease and abnormal left ventricular function was mentioned previously as initially showing better

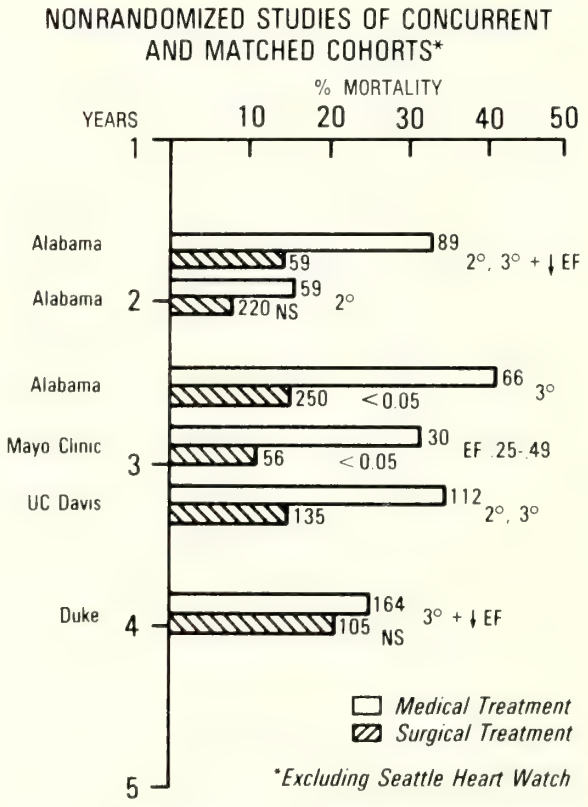

Figure 6.—Composite graph of the cumulative mortality from four nonrandomized studies of concurrent and matched cohorts. The number of patients in each group is indicated on top of the bar. 2° = double-vessel disease, 3° = triple-vessel disease, EF = ejection fraction, NS = not significant. (Alabama data from Kouchoukos et al,[65] Mayo Clinic from Vlietstra et al,[27] UC Davis from Vismara et al[66] and Duke from Rosati et al.[32])

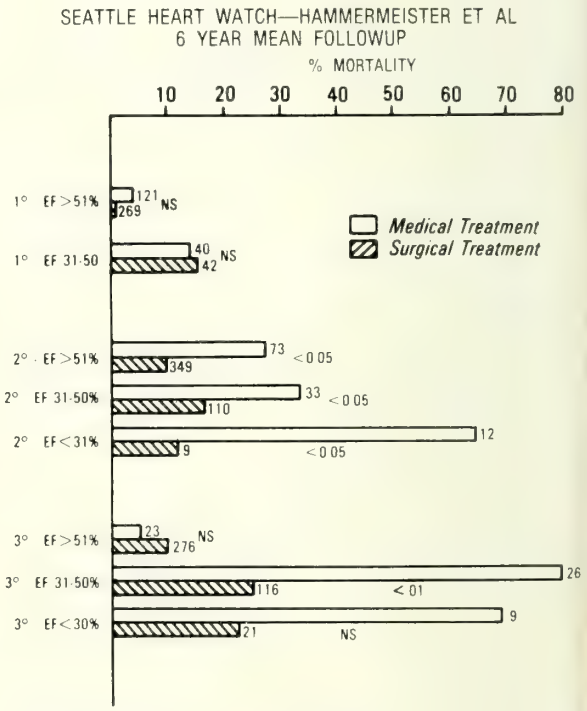

Figure 7.—Cumulative mortality for eight subgroups followed by Hammermeister et al[64] for a mean of six years. The number of patients in each group is indicated above the bars. 1° = single-vessel disease, 2° = double-vessel disease, 3° = triple-vessel disease, NS = not significant, EF = ejection fraction.

two-year survival with surgical therapy.[31] When 100 more patients were added to the subgroup and the patients observed for a cumulative mean of four years, the difference lost significance (Figure 6).[32] No other subgroups in the study have been reported to show survival differences.

Kouchoukos and co-workers[65] observed 499 surgical patients and 149 medical patients selected from those who had cardiac catheterization at the University of Alabama Medical Center between 1967 and 1975. The patients were not matched for invasively determined left ventricular function except in the high-risk group of 59 surgical patients and 89 medical patients with two- and three-vessel disease and enlarged hypokinetic left ventricles. The surgically treated group had a two-year survival of 86 percent, contrasted with the two-year survival of 67 percent for the medically treated group (significance not reported)

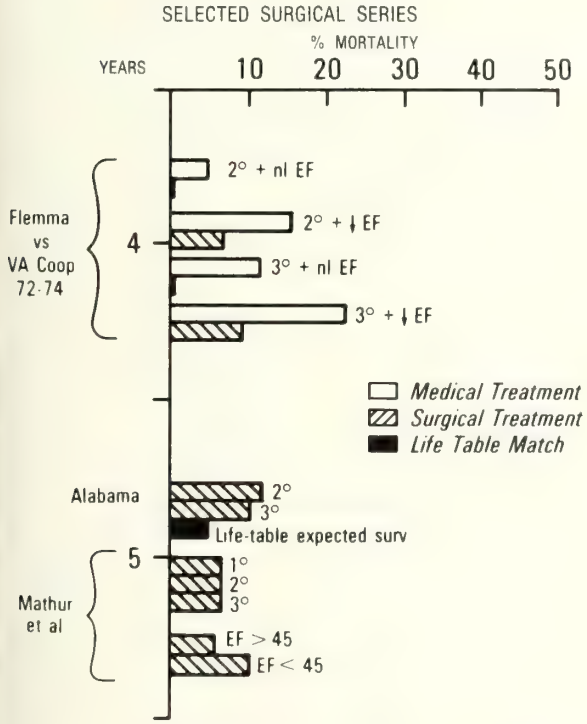

Figure 8.—Composite graph of selected series of surgically treated patients discussed in the text. The notations above the bars indicate the characteristics of the subgroup. 1° = single-vessel disease, 2° = double-vessel disease, 3° = triple-vessel disease, EF = ejection fraction. Flemma et al[48] contrasted four-year mortality of their surgically treated patients with comparable medically treated patients in the VA Cooperative Study. Rackley and colleagues[13] from the University of Alabama used life table expected survival for comparison with their surgically treated patients. Mathur et al[68] reported five-year survival data for surgically treated patients that are impressive even when they stand alone.

(Figure 6). In another report Kouchoukos, Zorn and Oberman reported that a subgroup of 164 surgically treated patients with triple-vessel disease and normal left ventricular function had a significantly greater five-year survival (94 percent versus 79 percent) than a concurrent and matched subgroup of 50 patients treated medically.[66]

Surgical Series Without Medical Cohorts

There are many published series of surgically treated cohorts with excellent survival. It was frequently assumed that the medical cohort from the Cleveland Clinic experience of the middle 1960's served as adequate controls to unmatched surgical series from the 1970's. When so compared, it appeared that surgical intervention substantially improved survival.[44,45,47,50] Because patients with coronary artery disease are so heterogeneous and the differences in survival between medically and surgically treated patients are so small, if present at all, surgical series without matched controls are of limited use. Nevertheless, authors have tried to establish comparability with medical series in a variety of ways.

Flemma and associates[48] compared the survival of 229 of their surgically treated patients who had operations during the same years as the VA Cooperative Study with the survival results of that study's medically treated patients. The perioperative mortality of the surgically treated patients was 0.4 percent, close to the lowest reported to date. The surgical subgroup with triple-vessel disease and normal left ventricular function had four-year survival of 100 percent, compared with survival in the medical series of 88 percent (Figure 8). If triple-vessel disease and abnormal left ventricular function coexisted, the surgical subgroup's survival was 90 percent and the medical subgroup's survival 77 percent. The surgical patients with double-vessel disease and abnormal function had a 9 percent better survival (93 percent versus 84 percent) at four years than the similar VA medical subgroup. The differences were not tested for significance. The subgroups with double-vessel disease and normal left ventricular function, and with single-vessel disease, showed no difference in survival.

Rackley and colleagues[13] at the University of Alabama compared survival of their surgical patients with that of age-, sex- and race-matched controls using the 1974 US Life Tables for the general population in an attempt to show that their surgical patients had a prognosis comparable

with that of the general population. Surgically treated patients with double- and triple-vessel disease had 87.6 percent and 88.9 percent survival, respectively, at five years' mean follow-up compared with the expected survival of 95 percent (Figure 8). The five-year survival of surgically treated patients with single-vessel disease was about 95 percent, the same as the matched general population and a medically treated group with single-vessel disease from the VA Cooperative Study.[29] Lawrie and co-workers[67] used a similar technique, comparing surgically treated patients from Baylor College of Medicine with life table controls, and showed similar results.

Mathur and colleagues[68,69] recently reported the five-year surgical survival of 846 patients at the St. Luke's Episcopal Hospital and Texas Heart Institute in Houston between 1973 and 1976. Survival for patients with one-, two- and three-vessel disease was 93.5 percent, 93.1 percent and 93.4 percent, respectively (Figure 8). For patients with ejection fractions greater than 45 percent the survival was 93.6 percent. For those with ejection fractions less than 45 percent the five-year survival was 89.1 percent. Of the group with triple-vessel disease and an ejection fraction less than 45 percent, 91 percent survived five years after operation.

Some of the surgical survival rates listed above are higher than those previously reported for either surgical or medical therapy. This suggests, but does not prove, that in some medical centers advances in surgical techniques during the 1970's may lead to improved survival with surgical therapy in selected subgroups. However, until such series are controlled with concurrent, matched medically treated groups, such conclusions are still tenuous.

Left Main Coronary Artery Disease

The increased survival of patients with symptomatic left main coronary artery disease treated surgically was detected early and readily.[41,70-72] The subgroup from the VA Cooperative Study with left main coronary artery disease had a four-year survival of 90 percent when treated surgically but only 60 percent when treated medically ($P<$ .001) (Figure 5).[9] The 59 patients in the ECSSG with left main coronary artery disease had a cumulative mean survival at five years of 93 percent when randomized to surgical therapy and a survival of 62 percent when randomized to medical therapy ($P=.037$) (Figure 5).[7]

Patients observed by Campeau and associates[73] at the Montreal Heart Institute were subgrouped not only by left main coronary disease but further subgrouped by ejection fraction. The five-year survival of the medically treated patients worsened progressively with worsening ejection fraction (Figure 5) while the surgically treated patients had an 80 percent survival or better until the ejection fraction was less than 45 percent. Conley and co-workers[74] used the Duke University Computer Registry to show that the three-year survival of medically treated patients with left main coronary disease was 25 percent if they were in a high-risk group with reduced left ventricular function or unstable angina and 74 percent if they were in the low-risk group without these factors (Figure 5). It is unclear from the two studies above whether moderate stenosis of the left main coronary artery (that is, 50 percent to 70 percent) is associated with the same poor prognosis as 70 percent or greater stenosis.[73,74]

Before 1972 the perioperative mortality of patients with left main coronary disease was about 10 percent to 20 percent.[41,73,75] Since 1972, however, the reported perioperative mortality has been about 2 percent to 6 percent.[13,37,41,73,75-77] Subsequent annual mortality has been about 1 percent to 2 percent.[13,76,77] Because survival after surgical treatment has consistently been superior to the reported survival with medical therapy alone, randomization of symptomatic patients with greater than 70 percent stenosis of the left main coronary artery to medical therapy alone no longer appears to be justified.

It has long been speculated that patients with so-called left main equivalent, proximal stenoses of both the left anterior descending and left circumflex coronary arteries, might carry the same poor prognosis as those with true left main coronary artery stenosis.[78] Subsets of patients with left main coronary disease and left main equivalent (as defined above) from the Duke University Computer Registry were found not to have equivalent five-year survivals.[79] The subset with left main coronary disease had a 36 percent five-year survival, contrasted with the 54 percent survival of the subset with left main equivalent. Furthermore, left main equivalent did not factor out as a significant variable affecting survival in a multivariate analysis ($P<.20$) while left main coronary disease was a highly significant independent baseline variable ($P<.001$). This is probably because sudden occlusion of the left main coronary artery lesion leads to catastrophic

results. While independent acute occlusions of the left anterior descending or circumflex coronary arteries are not well tolerated, they are probably less catastrophic than a left main coronary artery occlusion. Thus, patients with left main equivalent should be treated on the basis of other variables such as symptoms, left ventricular function and coronary anatomy.

Unstable Angina

Even the best study evaluating medical versus surgical therapy for unstable angina, the National Cooperative Study on Unstable Angina, was flawed by a 36 percent medical to surgical therapy crossover.[8] Nonetheless, the design of the study allows several conclusions. Nine cooperating American medical centers between 1972 and 1976 randomly assigned 288 patients without left main coronary lesions to medical therapy or urgent coronary bypass operation after initial medical stabilization. If symptoms persisted or worsened on medical therapy, then the patient was allowed to cross over to surgical therapy. The two-year mortality with medical therapy, 9 percent, was not nearly so bad as had been reported in the early 1970's before widespread and liberal use of long-acting nitrates and beta blockers.[80-83] The in-hospital mortality was 3 percent for the medically treated patients and 5 percent for the surgically treated patients. This decreased to 2 percent and 3 percent, respectively, in the latter years of the study. The late mortality at 30 months of follow-up was also similar at 7 percent and 5 percent, respectively, for medically treated and surgically treated patients. The in-hospital and late myocardial infarctional rates were also similar in the latter years of the study. There was a significantly higher prevalence of NYHA functional class III and IV angina in the medical group in the first year after randomization, but the difference disappeared by the second year as 36 percent of the patients had late bypass surgical procedure. There was no difference in working status between the two groups.

The impact of the medical to surgical crossovers on survival rates will never be known. However, the survival figures at 42 months of cumulative mean follow-up were the same for the subgroups of all patients randomly assigned to medicine, all patients randomly assigned to bypass operation, medical patients with later operation and medical patients without later operation. Thus, this study implies that medical therapy for unstable angina with the option of future bypass surgical procedure should symptoms persist or worsen results in morbidity and mortality at least as good as early surgical therapy after initial stabilization. A recently published nonrandomized data-bank study concludes, however, that early surgical therapy does result in a significantly better 40-month survival than medical therapy (91 percent versus 76 percent, $P<.025$).[84] The higher mortality in the medically treated group in the latter study (24 percent versus 9 percent) accounts for the difference in results between the two studies, so one should be suspicious that the nonrandomized design of the latter biased the results against medical therapy.

Comment and Conclusions

Most of the data reviewed reflect medical and surgical therapeutic methods used before 1975. The time lag of five years between a therapeutic intervention and the ability to assess the results of that intervention is one of the reasons that the results we have are so unclear and controversial. Since 1975 there have been objective improvements in short-term surgical results,[7,13-15,36,45,47-59] but it is unknown whether advances in medical therapy have had an equivalent impact on survival.[10-12]

Large epidemiologic studies have shown the heterogeneity of coronary artery disease by determining the relative impact of various baseline variables on survival.[18,19,22,63,64] Left ventricular function is the predominant factor affecting survival for both medically and surgically treated patients.[18,19] The number of major coronary arteries stenosed is the second most important factor for medically treated patients, but for surgically treated patients it ceases to be a significant factor affecting prolonged survival.[18,30,85] If diseased coronary arteries are left unbypassed, however, these "residual lesions" continue to influence survival postoperatively ($P<.002$).[85]

Multivariate analysis of variables that may affect survival is a means of showing apparent comparability between nonrandomized cohorts, or of analyzing whether surgical treatment itself was a variable predictive of increased survival in noncomparable groups.[20-22,64,86] Despite the elegance of this method in comparing nonrandomized cohorts, they could differ in some undefined variables that escape detection, so randomization is still the technique of choice. Even if randomized,

a rigorous analysis of comparability should be made.[20]

The Veterans Administration Cooperative Study was a milestone in showing that the survival of medically treated patients was not nearly so poor as had been previously believed. Surgical therapy in the cooperating VA hospitals between 1972 and 1974 improved six-year survival of the so-called high-risk patients only. The relatively poor surgical results limited the applicability of this study. The European Coronary Surgery Study Group observed patients with good left ventricular function only. It reported improved survival of patients with triple-vessel disease and left main coronary artery disease randomly assigned to surgical treatment.[7] Survival results for the 780 randomly assigned patients and 24,959 patients observed by registry as part of CASS have yet to be reported.[16,34-38]

Most of the recent and larger studies, recognizing the heterogeneity of coronary artery disease, have analyzed survival in subgroups defined by the number of diseased vessels and left ventricular function. No such study has shown improved survival with surgical therapy in subgroups with single-vessel disease regardless of left ventricular function. Subgroups with multivessel disease and normal left ventricular function have been shown to have better survival with surgical therapy in the triple-vessel disease group of the ECSSG trial[7] and in the nonrandomized studies by Hammermeister and colleagues[21,22,63,64,86] and Zorn and co-workers.[66] Subgroups with multivessel disease and abnormal left ventricular function, however, have had either significantly better* or a trend toward better survival with surgical therapy[9,30,32] in every study in which survival has been addressed in this so-called high-risk subgroup.

Only recently have factors other than left ventricular function and the number of diseased major coronaries been used to further characterize subgroups that could have survival differences in response to surgical or medical therapy. The ECSSG, for example, reported that in medically treated patients with double-vessel disease including the left anterior descending (LAD) coronary, a significant proximal LAD stenosis was associated with a worse survival than if the stenosis was distal to the first septal branch.[7,87] DeRouen and associates[22] recently characterized many different subgroups of patients that benefited from surgical therapy more than other subgroups. As described above, those with multivessel disease, an ejection fraction greater than 30 percent, age greater than 48, NYHA classes I and II angina and without heart murmurs, diuretic use, congestive heart failure, cardiomegaly or ventricular arrhythmias benefited more from surgical therapy than their counterparts from medical treatment.[22] The VA Cooperative Study defined a high-risk subgroup on clinical characteristics alone that showed a survival advantage with surgical therapy.[42]

Some centers have recently reported impressively high postsurgical survival rates, even in high-risk patients having triple-vessel disease and impaired left ventricular function.[48,68,69] Therefore, it is probable that future controlled studies will show large and unequivocally significant improvement in survival with surgical therapy in patients with double- and triple-vessel disease with, and possibly without, left ventricular dysfunction. However, current data suggest that for patients with both stable and unstable angina, improved survival over a five- to ten-year period is small enough, if present at all, that it probably should not be the predominant factor in determining whether or not an individual patient who does not have left main coronary artery disease should undergo coronary bypass operation. Rather, the prime consideration should remain the proved potential of the operation for improving a patient's quality of life by eliminating or lessening the severity of angina and reducing the need for antianginal medications.[5] Even this benefit, however, may be palliative for many patients because there is some evidence that the advantage of surgical therapy over medical therapy for relief of angina pectoris may be only temporary, lasting three to seven years.[7,14,88,89] More and more patients are requiring reoperation as their symptoms return so that it is not uncommon to see patients who have had two and sometimes three bypass operations.

*References 21, 22, 27, 48, 63-65, 86.

REFERENCES

1. Sabiston DC Jr: The coronary circulation. Johns Hopkins Med J 1974 Jun; 134:314-329

2. Miller DW, Ivey ID, Bailey WW, et al: The practice of coronary artery bypass surgery in 1980 (abst). Circulation 1980; 62(Suppl II):95

3. Adkins PC, Orthner HF: The Society of Thoracic Surgeons manpower survey for 1976: A summary. Ann Thorac Surg 1979 Nov; 28:407-412

4. Collins JJ Jr: The cost of coronary bypass surgery, *In* Hurst JW (Ed): Update II. The Heart—Bypass Surgery for Obstructive Coronary Disease. New York, McGraw-Hill, 1980, pp 271-280

5. King SB, Hurst JW: The relief of angina pectoris by coronary bypass surgery, *In* Hurst JW (Ed): Update II. The Heart—Bypass Surgery for Obstructive Coronary Disease. New York, McGraw-Hill, 1980, pp 71-83

6. Peduzzi P, Hultgren HN: Effect of medical vs surgical treatment on symptoms in stable angina pectoris. Circulation 1979; 60:888-900

7. European Coronary Surgery Study Group: Prospective randomized study of coronary artery bypass surgery in stable angina pectoris. Lancet 1980; 2:491-495

8. Russell RO Jr, Moraski RE, Kouchoukos NT, et al: Unstable angina pectoris: National Cooperative Study Group to Compare Surgical and Medical Therapy—II. In hospital experience and initial follow-up results in patients with one, two and three vessel disease. Am J Cardiol 1978; 42:839-848

9. Takaro T and participants in the VA Cooperative Study: Results of a randomized study of medical and surgical management of angina pectoris. World J Surg 1978 Nov; 2:797-807

10. Multicentre International Study: Reduction in mortality with long-term beta-adrenoceptor blockade: A multicentre international study. Br Med J 1977; 2:49-51

11. The Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981; 304:801-807

12. Weinblatt E, Ruberman W, Goldberg JD, et al: Prognosis of men after first acute myocardial infarction in the 1960's and 1970's: Search for a secular trend (abst). Am J Cardiol 1981; 47:487

13. Rackley CE: Prolongation of life after coronary artery bypass surgery at the University of Alabama Medical Center, *In* Hurst JW (Ed): Update II. The Heart—Bypass Surgery for Obstructive Coronary Disease. New York, McGraw-Hill, 1980, pp 151-158

14. Hall RJ, Mathur VS, Garcia E, et al: The prolongation of life by coronary bypass surgery, *In* Hurst JW (Ed): Update II The Heart—Bypass Surgery for Obstructive Coronary Disease. New York, McGraw-Hill, 1980, pp 175-204

15. Lawrie GM, Morris GC Jr: Improved survival after coronary bypass: A long-term perspective from Baylor College of Medicine, *In* Hurst JW (Ed): Update II. The Heart—Bypass Surgery for Obstructive Coronary Disease. New York, McGraw-Hill, 1980, pp 221-237

16. Kennedy JW, Kaise GC, Fisher LD, et al: Clinical and angiographic predictors of operative mortality from the Collaborative Study in Coronary Artery Sugery (CASS). Circulation 1981; 63:793-802

17. Murphy ML, Hultgren HN, Detre KM, et al: Treatment of chronic stable angina—A preliminary report of survival data of the randomized Veterans Administration Cooperative Study. N Engl J Med 1977 Sep 22; 297:621-627

18. Hammermeister KE, DeRouen TA, Dodge HT: Variables predictive of survival in patients with coronary disease—Selection by univariate and multivariate analysis from the clinical, electrocardiographic, exercise, arteriographic and quantitative angiographic evaluations. Circulation 1979; 59:421-430

19. Harris PJ, Harrell FE Jr, Lee KL, et al: Survival in medically treated coronary artery disease. Circulation 1979; 60: 1259-1269

20. Lee KL, McNeer FJ, Starmer FC, et al: Clinical judgment and statistics—Lessons from a simulated randomized trial in coronary artery disease. Circulation 1980; 61:508-515

21. Hammermeister KE, DeRouen TA, Dodge HT: Evidence from a nonrandomized study that coronary surgery prolongs survival in patients with two-vessel coronary disease. Circulation 1979; 59:430-435

22. DeRouen TA, Hammermeister KE, Dodge HT: Comparisons of the effects on survival after coronary artery surgery in subgroups of patients from the Seattle Heart Watch. Circulation 1981; 63:537-545

23. Bruschke AVG, Proudfit WL, Sones FM Jr: Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5-9 years—I. Arteriographic correlations. Circulation 1973 Jun; 47:1147-1153

24. Proudfit WL, Bruschke AVG, Sones FM: Natural history of obstructive coronary artery disease: Ten-year study of 601 nonsurgical cases. Prog Cardiovasc Dis 1978; 21:53-78

25. Bruschke AVG, Proudfit WL, Sones FM Jr: Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5-9 years—II. Ventriculographic and other correlations. Circulation 1973; 47:1154-1163

26. Gross H, Vaik AK, Cohen MV: Prognosis in patients rejected for coronary revascularization surgery. Am J Med 1978; 64:9-20

27. Vlietstra RE, Assad-Morrell JL, Frye RL, et al: Survival predictors in coronary artery disease—Medical and surgical comparisons. Mayo Clin Proc 1977 Feb; 52:85-90

28. Epstein SE, Kent KM, Goldstein RE, et al: Strategy for evaluation and surgical treatment of the asymptomatic or mildly symptomatic patient with coronary artery disease. Am J Cardiol 1979; 43:1015-1025

29. Detre KM, Murphy ML, Hultgren HN: Effect of coronary bypass surgery on longevity in high and low risk patients—Report from the VA Cooperative Surgery Study. Lancet 1977; 2:1243-1245

30. Read RC, Murphy ML, Hultgren HN, et al: Survival of men treated for chronic stable angina pectoris—A cooperative randomized study. J Thorac Cardiovasc Surg 1978; 75:1-12

31. McNeer JF, Starmer CF, Bartel AG, et al: The nature of treatment selection in coronary artery disease—Experience with medical and surgical treatment of a chronic disease. Circulation 1974; 49:606-614

32. Rosati RA, Lee KL, Mittler BS, et al: Does coronary surgery prolong life in comparison with medical management? Postgrad Med J 1976; 52:749-756

33. Gifford RH, Feinstein AR: A critique of methodology in studies of anticoagulation therapy for acute myocardial infarction. N Engl J Med 1969; 280:351-357

34. Killip T (Ed): National Heart, Lung, and Blood Institute Coronary Artery Surgery Study. Circulation 1981; 63(Suppl I):1-81

35. Zimmern SH, Rogers WJ, Bream PR, et al: Total occlusion of the left main coronary artery: The CASS experience (abst). Am J Cardiol 1981; 47:408

36. Gersh B, Frye RL, Kronmal RA, et al: Coronary angiography and coronary artery bypass surgery in elderly patients (abst). Am J Cardiol 1981; 47:494

37. Chaitman BR, Rogers WJ, Davis K, et al: Operative risk factors in patients with left main coronary-artery disease. N Engl J Med 1980; 303:953-957

38. Davis K, Kennedy JW, Kemp HG Jr, et al: Complications of coronary arteriography from the Collaborative Study of Coronary Artery Surgery (CASS). Circulation 1979 Jun; 59:1105-1112

39. Detre KM, Hultgren HN, Murphy ML, et al, in discussion, Campeu L, et al, Reference 89. Circulation 1979; 60(Suppl I): 28-30

40. Detre KM, Wright E, Murphy ML, et al: Observer agreement in evaluating coronary angiograms. Circulation 1975; 52 979-986

41. Takaro T, Hultgren HN, Lipton MU, et al: The VA cooperative randomized study of surgery for coronary arterial occlusive disease—II. Subgroups with significant left main lesions. Circulation 1976; 54(Suppl III): 107-117

42. Detre KM, Peduzzi P, Murphy ML, et al: Effect of bypass surgery on survival in patients in low- and high-risk subgroups delineated by the use of simple clinical variables. Circulation 1981; 63:1329-1338

43. National Institutes of Health Consensus-Development Conference Statement: Coronary-artery bypass surgery: Scientific and clinical aspects. N Engl J Med 1981; 203:680-684

44. Favaloro RG: Direct myocardial revascularization: A 10 year journey—Myths and realities (Louis F. Bishop Lecture). Am J Cardiol 1979 Jan; 43:109-129

45. Hurst JW, King SB III, Logue RB, et al: Value of coronary bypass surgery—Controversies in cardiology: Part I. Am J Cardiol 1978 Aug; 42:308-329

46. Pryor DB, Harris PJ, Lee KL, et al: The effects of crossovers on estimates of survival in medically treated patients with coronary artery disease (abstr). Am J Cardiol 1980; 45:455

47. Cohn LH, Boyden CM, Collins JJ Jr: Improved long-term survival after aortocoronary bypass for advanced coronary artery disease. Am J Surg 1975 Apr; 129:380-385

48. Flemma RJ, Mullen DC, Lepley D, et al: A comparative synchronous coronary surgery survival study. Ann Thorac Surg 1979; 28:423-428

49. Carey JS, Cukingnan RA, Groner GF: Veterans Administration cooperative study of surgery for coronary arterial occlusive disease: View from a noncooperating hospital. Circulation 1979 Aug; 60(Suppl I):30-33

50. Proudfit WL: The prolongation of life by coronary bypass surgery: Experience at the Cleveland Clinic, *In* Hurst JW (Ed): Update II. The Heart—Bypass Surgery for Obstructive Coronary Disease. New York, McGraw-Hill, 1980, pp 3-11

51. Hutchinson JE III, Green GE, Mekhjian HA, et al: Coronary bypass grafting in 476 patients consecutively operated on. Chest 1973 Dec; 64:706-710

52. Kloster FE, Kremkau EL, Ritzmann LW, et al: Coronary bypass for stable angina—A prospective randomized study. N Engl J Med 1979 Jan 25; 300:149-157

53. Greene DG, Bunnell IL, Arani DT, et al: Preservation of the myocardium by coronary bypass surgery: The effect on survival, *In* Hurst JW (Ed): Update II. The Heart—Bypass Surgery for Obstructive Coronary Disease. New York, McGraw-Hill, 1980, pp 159-174

54. Miller DC, Stinson EB, Doyer PE, et al: Current risk surrounding coronary bypass surgery (abst). Am J Cardiol 1981; 47:400

55. Manley JC, King JF, Assa J: Factors influencing results during 12 years of coronary artery bypass surgery in 7,362 patients (abst). Am J Cardiol 1981; 47:485

56. Vismara LA, Miller RR, Price JE, et al: Improved longevity due to reduction of sudden death by aortocoronary bypass in coronary atherosclerosis—Prospective evaluation of medical versus surgical therapy in matched patients with multivessel disease. Am J Cardiol 1977; 39:919-924

57. Marco JD: Myocardial perfusion by coronary artery bypass, *In* Hurst JW (Ed): Update II. The Heart—Bypass Surgery for Obstructive Coronary Disease. New York, McGraw-Hill, 1980, pp 13-31

58. FitzGibbon GM, Burton JR, Leach AJ: Coronary bypass graft fate—Angiographic grading of 1400 consecutive grafts early after operation and of 1132 after one year. Circulation 1978 Jun; 57:1070-1074

59. Hamby RI, Aintablian A, Handler M, et al: Aortocoronary saphenous vein bypass grafts—Long-term patency, morphology and blood flow in patients with patent grafts early after surgery. Circulation 1979 Oct; 60:901-909

60. Mathur VS, Guinn GA, Anastassiades LC, et al: Surgical treatment for stable angina pectoris—Prospective randomized study. N Engl J Med 1975 Apr 3; 282:709-713

61. Mathur VS, Guinn GA: Long-term follow-up (4-7 years) of a prospective study to evaluate surgical vs medical treatment for stable angina pectoris: Clinical status, exercise performance and survival (abst). Am J Cardiol 1979; 43:382

62. Kloster F, Morris C, Kanarek P: Influence of bypass surgery on mortality and morbidity in stable angina: A prospective randomized study (abst). Am J Cardiol 1980; 45:455

63. Hammermeister KE, DeRouen TA, Murray JA, et al: Effect of aortocoronary saphenous vein bypass grafting on death and sudden death—Comparison of nonrandomized medically and surgically treated cohorts with comparable coronary disease and left ventricular function. Am J Cardiol 1977; 39:925-934

64. Hammermeister KE, DeRouen TA, Dodge HT: Survival analysis in medically and surgically treated patients with coronary disease: A critical review and experience in Seattle Heart Watch, a nonrandomized series, *In* Hurst JW (Ed): Update II. The Heart—Bypass Surgery for Obstructive Coronary Disease. New York, McGraw-Hill, 1980, pp 239-253

65. Kouchoukos NT, Oberman A, Karp RB: Results of surgery for disabling angina pectoris, *In* Rahimtoola SH (Ed): Coronary Bypass Surgery. Philadelphia, F. A. Davis, 1977, pp 157-166

66. Zorn GL, Oberman A, Kouchoukos NT: Late results of operative and non-operative therapy in patients with three vessel disease and normal left ventricular contractile pattern (abst). Circulation 1979; 59 and 60(Suppl II):60

67. Lawrie GM, Morris GC Jr, Howell JF, et al: Improved survival after five years in 1144 patients after coronary bypass surgery. Am J Cardiol 1978; 42:709-715

68. Mathur VS, Hall RJ, Garcia E, et al: Improved longevity following coronary bypass (CAB) surgery: Is it real or is it an illusion? (abst) Am J Cardiol 1980; 45:418

69. Mathur VS, Hall RJ, Garcia E, et al: Prolonging life with coronary bypass surgery in patients with three-vessel disease. Circulation 1980 (Suppl I):90-98

70. Lim TS, Proudfit WL, Sones FM Jr: Left main coronary arterial obstruction: Long-term follow-up of 141 nonsurgical cases. Am J Cardiol 1975; 35:131-135

71. Talono J, Scanlon P, Meadows W, et al: Influence of surgery on survival in 145 patients with left main coronary artery disease. Circulation 1975; 51 and 52 (Suppl I):105-111

72. Greene DG, Bunnell IL, Arani DT, et al: Long-term survival after coronary bypass surgery. Buffalo General Hospital, State University of New York, Brochure for exhibit at American Heart Association Meeting, Miami, 1977

73. Campeau L, Corbara F, Crochet D, et al: Left main coronary artery stenosis—The influence of aortocoronary bypass surgery on survival. Circulation 1978; 57:1111-1115

74. Conley MJ, Ely RL, Kisslo J, et al: The prognostic spectrum of left main stenosis. Circulation 1978; 57:947-952

75. Cohen MV, Gorlin R: Main left coronary artery disease—Clinical experience from 1964-1974. Circulation 1975; 52:275-285

76. Lawrie GM, Morris GC Jr, Howell JF, et al: Improved survival beyond 5 years after coronary bypass surgery in patients with left main artery disease. Am J Cardiol 1979; 44:612-615

77. Loop FD, Lytle BW, Cosgrove DM, et al: Atherosclerosis of the left main coronary artery: 5 year results of surgical treatment. Am J Cardiol 1979 Aug; 44:195-201

78. Hutter AM Jr: Is there a left main equivalent? Circulation 1980 Aug; 62:207-211

79. Conley MJ, Behar BS, Harrell FE, et al: Prognostic significance of left main equivalent stenosis (abst). Am J Cardiol 1981; 47:408

80. Krauss KR, Hutter AM Jr, DeSanctis RW: Acute coronary insufficiency—Course and follow-up. Circulation 1972; 45, 46 (Suppl I):66-77

81. Gazes PC, Mobley EM Jr, Faris HM Jr, et al: Preinfarctional (unstable) angina—A prospective study—Ten year follow-up. Prognostic significance of electrocardiographic changes. Circulation 1973 Aug; 48:331-337

82. Lopes MG, Spivack AP, Harrison DC, et al: Prognosis of non-infarctional coronary care unit patients (abst). Am J Cardiol 1973; 31:144

83. Watkins C, Russell RO Jr, Rackley CR: Follow-up study of unstable angina in a myocardial infarction research unit (abst). Circulation 1972; 45, 46(Suppl II):23

84. Hultgren HN, Shettigar U, Miller C: Unstable angina: Effect of medical versus surgical therapy on survival and myocardial infarction (abst). Am J Cardiol 1981; 47:486

85. Lawrie GM, Morris GC Jr, Silvers A, et al: Residual lesions after coronary bypass: An important variable affecting late survival (abst). Am J Cardiol 1980; 45:418

86. Hammermeister KE, DeRouen TA, Dodge HT: Effect of coronary surgery on survival in minimally symptomatic patients. Circulation 1980; 62(Suppl I):98-102

87. Varnauskas E and the European Coronary Surgery Study Group: The effect of an obstruction in the proximal third of the left anterior descending artery on two year survival (abst). Circulation 1979; 59, 60 (Suppl II):250

88. Davidson DM, Lamb I, Schroeder JS: Long term results of coronary artery bypass for unstable angina: Mortality, myocardial infarction and angina (abst). Am J Cardiol 1980; 45:419

89. Campeau L, Lesperance J, Hermann J, et al: Loss of improvement of angina between 1 and 7 years after aortocoronary bypass surgery: Correlation with changes in vein grafts and in coronary arteries. Circulation 1979; 60(Suppl I):1-5

90. Loeb HS, Pifarre R, Sullivan H, et al: Improved survival after surgical therapy for chronic angina pectoris—One hospital's experience in a randomized trial. Circulation 1979; 60(Suppl I): 22-28

Clinical Management Conference

EUGENE D. ROBIN, MD
and
A COMMUNITY HOSPITAL MEDICAL STAFF

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Refer to: Robin ED: Interstitial lung disease in an elderly woman —Clinical Management Conference, Stanford University School of Medicine. West J Med 1982 Apr; 136: 309-317

Interstitial Lung Disease in an Elderly Woman

This is a Clinical Management Conference (CMC) presented at a community hospital. It differs from conventional teaching conferences in that (1) the focus of analysis is direct patient benefit and diagnosis is regarded as a secondary process, (2) it seeks to provide an understanding of logical approaches to patient management while confronted with numerous uncertainties caused by an inadequate scientific base, (3) there is no absolute answer provided and (4) the conference involves the entire audience of physicians as direct participants.

EUGENE D. ROBIN:* The patient was an 81-year-old woman with a history of rheumatoid arthritis, currently inactive, and three years of progressively severe shortness of breath. She entered the hospital because of a substantial worsening of her shortness of breath over the preceding week. There was no smoking history and she had done well until three years before admission when she noted some progressive but relatively mild shortness of breath. Three years before admission she could walk a level two blocks, but her exercise tolerance decreased so that at the time of admission she became dyspneic merely walking across the room. She had a history of congestive heart failure and chronic atrial fibrillation. She stated she had no fever, chills, productive cough, wheezing, hemoptysis, tuberculosis or asthma. She had two-pillow orthopnea. In her past medical history, as previously noted, she had rheumatoid arthritis that had been treated with gold. There was no family history of lung disease and she was taking digoxin (0.125 mg a day); furosemide (Lasix), about 40 mg a day, and two tablets of buffered aspirin three times a day. Her travel history was limited to the Philadelphia area.

And now I would like to ask you a general question. This is an 81-year-old patient; is there any difference in the intensity of workup you would do on her as compared with, say, a 40-year-old patient with the same history?

PHYSICIAN A: *No. There should be no difference.*

DR. ROBIN: Would you defend your rather dogmatic "no"?

PHYSICIAN A: *Well, she might be a young 81 and the other might be an old 40, so age is irrelevant.*

DR. ROBIN: You think it's completely irrelevant?

PHYSICIAN A: *Well, not exactly. But it depends on the patient. I think it's what she wants to do, and how far she wants to go.*

DR. ROBIN: You are beginning to put conditions on your original answer. Suppose this is an average 81 year old.

PHYSICIAN A: *Age per se is not a modifying factor.*

*Professor of Medicine and Physiology, Division of Respiratory Medicine.

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DR. ROBIN: How about age 91? Not a modifying factor? Age 101? Not a modifying factor. The workup and management should not be different?

PHYSICIAN A: *Maybe.*

DR. ROBIN: And if this were Thomas Parr, age 179? Do you all know the story of Thomas Parr? As we've gotten off on a rather impromptu note, I may as well tell you. Thomas Parr was an Englishman who lived in a small village and was said to have survived to the age of 179, outliving seven reigning monarchs of England and eight wives. He was discovered by William Harvey (the physician who originally described the circulation) and taken to London. It was said that he spent three weeks there. Unaccustomed to the wines and food in London, Parr speedily became ill and died. He was regarded especially by Harvey, who was very influential, as such an unusual paragon that he was buried in Westminister Abbey. It turned out that Thomas Parr was actually a father and son who had pulled the wool over everyone's eyes, including William Harvey. I suspect that he (the son) is not the only con man buried in Westminster Abbey.

PHYSICIAN B: *Are you the same fellow who's been here every time?*

DR. ROBIN: No, I'm really my son. Anyway, let's get back to being serious. So at 101 you'd begin to pause about the intensity of workup?

PHYSICIAN C: *Well, I think in an 81-year-old person the likelihood of coronary artery disease is so great that one could expect that she was suffering from congestive heart failure on the basis of coronary artery disease, namely arteriosclerotic heart disease, either silent or with a past history of myocardial infarction evident on cardiography. So I think the workup of this patient would be somewhat light. I don't think I'd overlook other causes of congestive heart failure, such as hyperthyroidism, possibly even rheumatoid arthritis causing some pulmonary congestion or valvular heart disease, but I also don't think I'd go searching for "zebras" like lupus or some of the other collagen vascular diseases.*

DR. ROBIN: Is there other discussion, pro or con? All who would manage this lady all out because she might be a young 81 year old, raise your hands. [*No physicians, including physician A, vote to support a non-age-factored approach.*]

DR. ROBIN to PHYSICIAN A: You should raise your hand.

PHYSICIAN A: *I thought you were raising a theoretical question involving all patients.*

DR. ROBIN: I am raising a theoretical question that involves many patients. And that is, should age be an important factor in determining the intensity of diagnostic workup?

PHYSICIAN A: *Yes.*

DR. ROBIN: Is there anyone who disagrees with that? We had previously discussed an 83-year-old lady and formulated some general guidelines to the management of the very old. Using the mean age of survival of American women, our patient would have minus four years to live. If you look at the actuarial tables, they show that having lived to 81, because of the shape of the survival curves, the patient would be expected to survive for six more years. On a statistical basis, you are outlining management for a survival between minus four and plus six years. As a result, your management should be quite different in an 81 year old than in a 40 year old. (Even ignoring the fact that much of what we do in younger people is tolerated better by them than it is by old people), the aggressiveness with which you manage older patients is less. I believe it's incorrect to simply say, "If the patient is physiologically younger than his or her chronologic age, we're going to go all out."

PHYSICIAN D: *What if you have a 40-year-old patient with cirrhosis who is very low in social class and probably isn't going to make it anyhow? In other words, are you setting any standards based on the social value of the patient?*

DR. ROBIN: You will have to set your own standards. But let's consider the 40-year-old patient with cirrhosis. I would consider that you should do the best you can for him, to provide as happy and productive a life for him as you can. And I would try to do the same for the 81-year-old woman. This may mean different things for each patient. For one thing, it depends on what each wants. But it is, I believe, an error to say that if you've managed somebody who's 81 and can expect four or five years of additional life, that you'll do the same kind of planning that you do for somebody at age 40.

PHYSICIAN D: *Now that old people are being treated with kidney machines, cobalt and so*

forth, how can we philosophically exempt any person from the same intensity of care given the young?

DR. ROBIN: The point is that you try to do the best you can for each patient based on an individual analysis. The experience with renal dialysis has been quite interesting. Before the federal government started paying for dialysis, as you know, hospitals with dialysis units had committees. These committees included religious leaders, community representatives, nurses and physicians. When somebody was proposed for dialysis there was a long discussion about the social value of the person, whether to take a 60-year-old or older person in preference to a young patient and how reversible was a person's disease. Then the federal government started paying for dialysis and now even if you're 81 years old you get on the machine. Most of the philosophy seems to have vanished. What I'm suggesting is that we can be more thoughtful in our approaches. And it isn't correct to say that you can ignore the ravages of age, whatever they may be. When you say here's a person with cirrhosis and his social contributions are negligible or close to it, would you really use that in your evaluation?

PHYSICIAN D: *I think each one will have to make that decision for himself.*

DR. ROBIN: OK. Well, I have decided that for myself. I don't think that substantial neglect is an appropriate penalty for people who have chronic alcoholism.

PHYSICIAN E: *How do you feel about the medical cost of caring for social misfits?*

DR. ROBIN: Given the abundant riches of this country, and especially with a more sensible approach to patient care, one can provide optimal care for patients even if this seems to be not in society's best interest.

Now there's a second question I wanted to ask about our patient. But before I do, is there general agreement that if this were your patient a red light would flicker off and on a few times indicating that she is 81 years old and you are going to be substantially more conservative with her than one might be with somebody who's 40?

PHYSICIAN F: *Maybe it's pink lights for me.*

DR. ROBIN: OK. Pink lights. That's fair enough. Now the second question is, can we agree that there is clearly one disease or one disorder at least partially responsible for her dyspnea? Could I have a volunteer?

PHYSICIAN F: *Congestive heart failure.*

DR. ROBIN: Good, she has congestive heart failure. On physicial examination she was seen to have cervical venous distention and she apparently had atrial fibrillation. S1 and S2 were normal and there was a grade 2 of 6 systolic ejection murmur. The chest was resonant on percussion. There were bilateral crackles heard and she had no E to A changes, indicating that she probably did not have consolidation. The abdomen was soft, there was no hepatosplenomegaly felt and the extremities showed no nodules. Roentgenograms of the chest showed some degree of cardiomegaly and nodular diffuse interstitial and alveolar infiltrates. These findings were dramatic and were not seen on x-ray studies of the chest a year ago. The laboratory studies gave the following values: leukocyte count was 7,200 per cu mm, hemoglobin was 13.9 grams per dl and hematocrit was 41 percent. She had fairly severe hypoxemia with a relatively normal carbon dioxide partial pressure (P_{CO_2}). Her sodium and potassium were normal but blood urea nitrogen was moderately elevated. Her serum glucose was a little elevated, as was her sedimentation rate. She had a total eosinophil count of 264 per cu mm.

Now for some specific questions. Let's begin with the total eosinophil count. Would you have ordered the test and how do you interpret it? Can I have a volunteer? Is there an allergist in the house?

PHYSICIAN G: *The total eosinophil count sometimes is used to evaluate the adrenal glands and if you're thinking of hypercorticism you should have very few eosinophils. The other use for it is, as you mention, allergy, but it's one of those tests that you can really derive from the complete blood count* (CBC) *by multiplying the leukocyte count times the percentage of eosinophils. If you've got maybe two or three* CBC's *you could get a feel for whether a patient has eosinophilia or not.*

DR. ROBIN: That's not entirely correct.

PHYSICIAN G: *Why not?*

DR. ROBIN: First of all, total eosinophil counts are also used to indicate the activity of bronchial asthma. There is a substantial relationship between the total eosinophil count and the total airway resistance. Pulmonary physicians—not uncommonly in bronchial asthma—measure the total

eosinophil count to get an index of how the patient should be treated, particularly with steroids. It's also used in patients who have hypersensitivity pneumonitis, because there may be substantial elevation of the total eosinophil count. And I guess the question I'm asking, because I'm pretty sure that was the context in which this was ordered, is, is there anything about this patient that sounds like bronchial asthma?

PHYSICIAN G: *No, there isn't.*

DR. ROBIN: And if this patient had bronchial asthma or hypersensitivity pneumonitis, particularly hypersensitivity pneumonitis, how would the patient have been treated? What's the conventional treatment for patients with hypersensitivity pneumonitis who are as symptomatic as this one?

PHYSICIAN H: *Steroids.*

DR. ROBIN: Steroids. And suppose the eosinophil count is normal, does that stop you from using steroids in hypersensitivity pneumonitis? The answer is no. And then I think one should at least entertain the argument that if you diagnosed hypersensitivity pneumonitis and used steroids, independent of the eosinophil count, you should not have ordered it. If it were normal you would treat with steroids and if it were elevated you would treat with steroids. Now, let me argue with your second statement, because we want to use these sessions to review general medicine. It's true that if the patient has a substantial increase in total eosinophil count, you can use the leukocyte differential. If the eosinophil count is in a borderline range, which is somewhere between 300 to 500 per cu mm, that approach is not accurate. When the smear is made, the eosinophils are pushed out toward the margins of the blood film. It's become traditional for technicians to count one eosinophil in 100 cells and multiply by 150. That is, unless major eosinophilia is present, you're unlikely to have it picked up by using the differential, and if you want to know about moderate increases in the eosinophil count you ought to get them directly counted. Do you do total eosinophil counts here?

PHYSICIAN I: *Yes.*

DR. ROBIN: Fine. The more important point is that it's difficult to see in this patient how the measurement would assist in management. An antinuclear assay showed a homogeneous pattern at a dilution of 1 to 40. Could I have a volunteer who would have ordered this study? No one? Who would not have ordered this study? Could I ask you to tell us why you wouldn't have?

PHYSICIAN I: *I think that looking for a collagen-type or a hypersensitivity disease, when you have a strong feeling that she does not have such a disorder, is not useful, and the likelihood of finding it is not that great . . .*

DR. ROBIN: I see. Suppose you had a strongly positive finding, would it have changed your form of therapy?

PHYSICIAN I: *No.*

DR. ROBIN: OK. Now let me ask you a question. Deep in your heart, and I'll ask it of the group, if this patient came in here and someone had the thought that the patient might have collagen vascular disease, how many would have ordered the antinuclear antibodies, even though it's clear that it would be difficult to use in management?

PHYSICIAN J: *I think if you'd thought of it, you'd probably order it. It would be nice to say that you'd thought of it.*

DR. ROBIN: It would be nice for whom?

PHYSICIAN J: *For yourself.*

DR. ROBIN: I would guess that the central issue is whether it would be *nice* for the patient. Her rheumatoid factor was 1 to 640. Let me ask you as a group again, how much help is that in the management of the patient? And how many of you would have ordered it? [*No hands are raised.*] Isn't there anyone who would have ordered it?

PHYSICIAN K: *I would not have. I'm assuming from the history, that of rheumatoid arthritis, that the test was done, and I'm making the assumption that there was a positive test result or several in the previous year.*

DR. ROBIN: Perhaps. I think the reasoning went something like this: Here's a patient with grossly abnormal findings on an x-ray study of the chest. Could the diagnosis be rheumatoid lung? If I find a high titer, it'll tend to confirm my impression that the patient has rheumatoid lung. I doubt that the analysis went as follows: The measurement will help in the specific management of the patient.

PHYSICIAN L: *Were all the tests ordered at the same time?*

DR. ROBIN: Roughly, yes.

PHYSICIAN L: *Within the first few days?*

DR. ROBIN: Within the first week of the patient's

admission. She was now being studied for the cause of the increased dyspnea and the cause of changes on her chest x-ray. I'll skip an analysis of the creatinine; the creatinine phosphokinase (CPK) I suppose was ordered because they thought of diffuse muscle disease or because they thought that she had a recent myocardial infarction. The plasma digoxin level was 1.1 ng per ml. Is there a cardiologist in the house?

PHYSICIAN K: *I'm sort of a cardiologist.*

DR. ROBIN: Would you have ordered a digoxin level?

PHYSICIAN K: *Probably. Particularly with old patients, it's difficult to judge the state of digitalization.*

DR. ROBIN: And you would have used it in the decision-making process by saying maybe her recent increase in dyspnea is related to inadequate digitalization or to digitalis toxicity and therefore the measurement would be useful in management?

PHYSICIAN B: *But what about her fibrillation? Isn't the heart rate an index of the digitalis status?*

PHYSICIAN K: *Yes, qualitatively, but not quantitatively. As a general rule, more accurate information is obtained from digoxin levels.*

PHYSICIAN B: *OK, but taking the other side of the coin, if the patient's rate of ventricular response is 70 to 100 per minute, could you assume that she's adequately digitalized, and if not, conclude that her digitalis status is suboptimal? I guess you could assume that she was not underdigitalized anyway; you might not be able to assume that she was not overdigitalized.*

PHYSICIAN K: *Heart rate data are inadequate. There's a poor correlation. If you feel more comfortable with heart rate, OK, but it's not a good index.*

PHYSICIAN L: *Going back to the patient's well-being, because digitalis is one of the common causes of death in the elderly, I think it's in her interest to get a level and find out where you're at.*

DR. ROBIN: Yes, that would be my reaction. In an 81-year-old patient cardiac glycosides are hazardous. Now the question of how technically adequate digoxin blood levels are and the relationship between plasma levels and myocardial levels is obscure. But I think that obtaining the level was a fairly thoughtful thing to do.

The total complement was 40, and how many of you would have ordered this test? Let's hope no one would have. It's been alleged that decreases in complement (a) are characteristic in some of the collagen diseases, particularly lupus, and (b) that the lower the values are, the more active the disease is and the more you're inclined to treat. But that's debatable because if you have a patient with full-blown symptomatology of lupus, whether the complement is up, normal or down, you will treat the patient. Again, even granting that it's technically correct in measurement, it doesn't do very much for the decision-making process. Is there anyone who objects to that statement? Is there an immunologist in the house?

PHYSICIAN M: *I would object in that I think in lupus, a low complement level would be useful in judging the response to therapy.*

DR. ROBIN: How much would you be influenced?

PHYSICIAN M: *I think that I would push therapy until complement levels came back up.*

DR. ROBIN: Well, I'd like to suggest that you're probably pushing a test harder than it deserves to be pushed. Clearly we have a difference of opinion. I can't pound on a table and say that my view is correct. If you have enough confidence in complement levels so that you would in the last analysis base a decision to a substantial degree on that test, then you should order it and follow it. You also have an additional responsibility, which is, incidentally, to make certain that the test is being done properly at the institution where it's being done because such tests have substantial technical errors. I don't have that degree of confidence in complement levels, probably not having looked at the same segment of literature as you, so I feel I would be entitled not to order it. I think both of us would agree that if you order it, you should order it thoughtfully, not because you have a patient who *might* have collagen vascular disease.

We measured the patient's serum IgG, IgA and IgM. Let me ask you two questions about that. One is, how helpful are the measurements of immunoglobulin levels in the diagnosis or management of 81-year-old patients with diffuse interstitial lung disease? Are they really all that useful in anyone unless you have a strong sus-

picion that you may have an immunoglobulin deficiency with a history of recurrent infections?

PHYSICIAN N: *They're very useful in very young patients with a diagnosis of recurrent infectious disease.*

DR. ROBIN: Certain types of infectious diseases. Can anyone stretch this usefulness to make this patient young enough or infected enough so that those tests would be useful? I don't think you can. The next question I want to ask you is, are these measurements available here?

PHYSICIAN N: *Yes.*

DR. ROBIN: Skin tests were done. The purified protein derivative (PPD) was negative and the test for *Candida albicans* was negative. Could I have an advocate for skin testing in this patient?

PHYSICIAN O: *I think* PPD *might be useful.*

DR. ROBIN: Yes. I think it is possible that this is tuberculosis (TB) in the aged. The test is minimally invasive and has a low cost. TB is one of the diseases that should be considered in older patients who have a recent exacerbation of symptoms and substantial diffuse changes on the chest film.

PHYSICIAN O: *The* PPD *response might help if it was negative. However, it might be positive because many patients have positive tests related to old inapparent infection.*

DR. ROBIN: Not quite true. Negativity may be related to the progressive anergy that occurs with aging. Incidentally, zinc tends to restore skin test reactivity in the aged. The population of old patients with positive skin tests for tuberculosis is progressively decreasing. As a result, a positive skin test assumes greater importance.

PHYSICIAN P: *Of course, you already have a total eosinophil count . . .*

DR. ROBIN: I'd rule out active tuberculosis on another basis except perhaps in the aged. If she had a lung full of tuberculosis she would have a high fever, systemic symptoms, weight loss and so on, so I don't think tuberculosis is likely. A gallium scan of the chest was normal. Do you do gallium scans here?

PHYSICIAN K: *Yes.*

DR. ROBIN: And can you tell me why they might have ordered a gallium scan? And what good gallium scanning of the chest is? Do we have a radiologist or a representative of the gallium scanning division? [*No response.*] I'm reasonably certain that I know why the test was performed. It's been alleged that in interstitial lung disease, particularly interstitial lung disease of the kind that is called usual interstitial pneumonia (UIP), you can determine activity of the disease by showing an accumulation of gallium in the lung. The records for this use are poor and it's not at all clear that if the gallium lung scan were positive you'd go ahead and use steroids or that if the gallium lung scan were negative you wouldn't use steroids. The implication has been that determining activity by a gallium scan helps you in deciding whether or not to give steroids; that's an uncertain assumption and I don't think that the world of interstitial lung disease would be all that much impoverished by not ordering gallium lung scanning.

The patient had an echocardiogram with a moderate to large posterior and a small anterior pericardial effusion. Could I ask our cardiology consultant, is there ever an echocardiogram that doesn't show at least a 50 ml posterior pericardial effusion?

PHYSICIAN K: *Yes.*

DR. ROBIN: Are there many?

PHYSICIAN K: *No.*

DR. ROBIN: She had concentric hypertrophy of the left ventricle, left atrial enlargement and mitral valve prolapse. May I ask you, would you have obtained an echocardiogram on this patient?

PHYSICIAN K: *Probably not. Not at 81.*

DR. ROBIN: If you have a large posterior pericardial effusion, your echocardiogram has given you a "zebra." You've found something that was unexpected, something that might be treated with benefit to the patient. Would you go ahead on the basis of an echocardiogram and tap her pericardial effusion?

PHYSICIAN K: *I wouldn't assume she had a pericardial effusion.*

DR. ROBIN: I see. And therefore you would have treated her congestive heart failure and, if she still had a persistent pericardial effusion, considered additional steps.

PHYSICIAN K: *Yes.*

DR. ROBIN: You must be correct because your reasoning agrees with mine. Would you fill us in on the present status of mitral valve prolapse,

that is, how significant a disease is it in the huge number of patients who have been described as having this abnormality?

PHYSICIAN K: *A large number of young, probably normal patients show mitral valve prolapse. We say that there are instances when the prolapse may be associated with sudden death, but these are rare. I wouldn't say it was totally a benign disease but it's frequently found in normal patients in the general population.*

DR. ROBIN: If you were doing a routine cardiac checkup on a 21-year-old woman, would you look for mitral valve prolapse so that you could tell her that she may die suddenly?

PHYSICIAN K: *No.*

DR. ROBIN: So you would not.

PHYSICIAN K: *No. Not unless she were symptomatic or had some other problem or complications.*

DR. ROBIN: I see. Is it unfair of me to suggest that we have had an iatrodemic (a plague caused by physicians) of mitral valve prolapse, with thousands of subjects being labeled as having a potentially lethal disease when, in fact, most of them were in no danger?

PHYSICIAN K: *Right.*

PHYSICIAN Q: *I think the echocardiogram created the disease. Did this not originate at Stanford?*

DR. ROBIN: I acknowledge that Stanford was one of the centers that helped create the so-called disease. I just want to be certain that everybody now knows that echocardiography has its own area of problems. Even three or four years ago, when you received a report that indicated the presence of mitral valve prolapse, you were concerned, and this concern was transmitted to the patient. Most of that was unwarranted. The patient has a cardiac scan with no evidence of focal wall abnormality and the study was considered to be normal. I'd like to ask a noncardiologist, suppose this patient were 40 years old and presented in exactly the same way. Would you have done a coronary arteriogram?

PHYSICIAN R: *I think I'd be tempted to do so. Severe heart failure in a 40 year old, who's really halfway through life, would not be inappropriately further investigated on the possibility that it's treatable. A 40-year-old patient has a long life to live, and I think I'd give him the benefit of possible surgery. Obtaining coronary arteriograms is not illogical.*

DR. ROBIN: Now, given that the patient is 81, could I ask you, sir? . . . You wouldn't.

PHYSICIAN S: *No, I would not.*

DR. ROBIN: So you'd say even if she was young and healthy for her 81 years, you wouldn't suggest she have a coronary arteriogram.

PHYSICIAN S: *No.*

DR. ROBIN: Now, another question that's frequently raised and was as a matter of fact raised in this patient, was whether an endocardial biopsy should have been done. Let's make the patient 40, what are the indications for endocardial biopsy?

PHYSICIAN K: *Heart transplant.*

DR. ROBIN: Well, let's leave heart transplant out of it and limit ourselves to myocardiopathies.

PHYSICIAN T: *Endocardial biopsy may be very helpful diagnostically.*

DR. ROBIN: I see. And which diseases might you find that are treatable which you would not detect by other means?

PHYSICIAN U: *Chagas.*

DR. ROBIN: Would you tell me the specific treatment for Chagas' disease?

PHYSICIAN U: *I don't know.*

DR. ROBIN: I don't know either. What diseases of the myocardium might you find on myocardial biopsy that you wouldn't suspect otherwise and that would provide a substantial plus in terms of finding a form of treatment for the patient? The only one I know of is sarcoid. The number of times that that's happened per number of biopsies is so small, I don't consider that a substantial reason for routine biopsy.

Now let me talk about what is for me a sensitive point. The patient had extensive pulmonary function studies. Should these have been ordered? The answer is a clear-cut no. These tests were a waste of her time and her energy. In fact, she was so breathless that she couldn't even perform a single breath measurement of her diffusing capacity. The patient underwent bronchoscopy, which revealed chronic bronchitis; cytology revealed no evidence of a malignant lesion and acid-fast cultures were negative. The justification for the bronchoscopy is not clear to me. She may well have undergone bronchial lavage with mea-

surements of cell population in the lavage fluid and measurement of immune globulins. This has been advocated as part of the workup in patients with interstitial lung disease. As these measurements cannot be accurately translated into effective management decisions, I would not have obtained them. I know of no evidence that when the cell population consists of neutrophils or lymphocytes or whatever, giving or not giving steroids is indicated. I know of no evidence that treatment guided by the results of lavage improves survival or life-style. She was presented to me because I was a visiting professor and her physicians wanted to know whether I would recommend transbronchial lung biopsy or an open-lung biopsy. The more astute of you can guess that I said no.

PHYSICIAN V: *Would you look at this case differently if this were in a teaching hospital versus a community hospital?*

DR. ROBIN: No.

PHYSICIAN W: *Well, don't you think it's because of your visit to this Philadelphia ivory tower that all these tests were done?*

DR. ROBIN: No. This was not an ivory tower. It was a community hospital. Moreover, I would guess that the workup was not too different from those done at most community hospitals.

PHYSICIAN W: *They have to answer for every test in case the professor questions them. They don't want to be caught flat-footed without having done the test so they, as you say, use a shotgun approach and every conceivable test is done in medical schools today just so that the one that might be asked about is not forgotten.*

DR. ROBIN: Yes. You're saying the type of approach used in this patient is used in teaching hospitals to please the professor. The house-staff does not want him to come in the next morning and say, "What?! You didn't order the serum rhubarb?! Don't you know that in the *Annals of Internal Medicine* two months ago there was an article showing that serum rhubarb values are distinctly elevated in all patients with ainhum?" I admit that's an important factor in the extensive overuse of diagnostic studies. But I don't believe that community physicians practice all that differently. We are all offspring of the same medical education system.

PHYSICIAN X: *Perhaps the medical students, the trainees, should be rewarded for* not *ordering the tests.*

DR. ROBIN: They should be given credit for the preciseness of their intellectual reasoning. If you will a priori analyze the ordering of a given test and say, "If the test is positive this is what I'll do with the data, if the test is negative that is what I'll do and if it's indeterminate this is what I'll do," and if you convince yourself that the test will be useful in patient management, I won't quarrel with obtaining it. What I quarrel with is to go ahead and order tests in which there is no clear-cut analysis of what's going to be done with the data. I would submit that that's poor patient care.

I was asked to advise her physicians whether either a transbronchial lung biopsy or an open-lung biopsy should be performed. May I ask how many of you at this point would have opted for obtaining lung tissues by biopsy? [*Approximately 40 percent of the assembled physicians voted for lung biopsy, approximately 40 percent voted against lung biopsy, approximately 20 percent abstained.*] I advised against lung biopsy based on the following analysis. What were the reasonable possibilities to explain her increased dyspnea and interstitial lung disease? One possibility was that the patient had increasing degrees of pulmonary edema related to heart failure. Such a diagnosis is difficult to make on lung biopsy. In any case both diagnosis and treatment are best made by increased dosage of diuretic drugs, manipulation of digoxin, afterload reduction, and so forth. A second possibility was that she had some kind of treatable infection, say tuberculosis or fungal disease. If this was the case in a women without systemic signs, you should be able to make the diagnosis noninvasively, that is, by sputum samples and the like. I would not biopsy her for that reason. The workup did not elicit known infections and, therefore, at least at this point in her illness, the possibility of treatable infection was remote.

A third possibility was that she had a malignant tumor, for example, alveolar cell carcinoma, which is associated with dyspnea and chest x-ray findings similar to hers. If that were the case, it would make little difference. One could reasonably wait until the process declared itself without a lung biopsy. A fourth possibility was that she had rheumatoid lung, in which case you would try steroid therapy. A fifth possibility was that

she had UIP or desquamative interstitial pneumonia, in which case steroids would be administered. I would be willing to try steroids empirically after treating her heart failure without having the security of a tissue diagnosis. I would administer these for a month to six weeks and if there was no improvement, stop the steroids.

A sixth possibility was that the patient had hypersensitivity pneumonitis. In this form of the disease, the patient would be treated with steroids. A seventh possibility was that the patient had collagen vascular disease, in which case the patient would be treated with steroids. The eighth possibility was that an unexpected disorder could be found for which specific therapy might be available, say lymphangiomyomatosis. I would submit that to justify biopsy by raising the possibility of finding a so-called zebra is not good medicine. Using such an approach, one could justify doing every procedure on every patient. It is always possible that one will come up with an unexpected finding that can be used to benefit the patient. Finally, it is likely that no diagnosis would emerge from the biopsy and the patient would have to be treated without one. (This happens in about 40 percent of patients who have transbronchial lung biopsy and in perhaps 20 percent who have open-lung biopsy.) The treatment would be steroids.

It has been stated that making a diagnosis in patients with diffuse interstitial lung disease is critical, but the data base for this assertion is not available. In fact, no careful study has been provided that estimates the therapeutic efficiency of lung biopsy in patients of this type.

In any case, the patient was treated intensively with diuretic drugs, her dyspnea lessened and there was substantial but incomplete clearing on the chest film. As I don't know the ultimate outcome of the patient, it is not possible to decide whether I was correct or incorrect.

PHYSICIAN Y: *Would you have tried immunosuppressives in this patient if steroids failed?*

DR. ROBIN: I would consider their use with some degree of hesitancy and perhaps would reconsider the question of lung biopsy at that point.

PHYSICIAN Z: *How about antibiotics?*

DR. ROBIN: The possibility of a bacterial infection, the usual kind of bacterial infection, was essentially nil. If her lung disease progressed and I was convinced that it was in her best interest to attempt to make a specific diagnosis, then a month later I might have recommended a lung biopsy. For all I know she may have undergone lung biopsy.

Summary

In summary, this was an 81-year-old woman with severe dyspnea and interstitial lung disease. She had a vast array of studies, most of which were nonfocused and unlikely to provide specific insight into treatment. The question of lung biopsy was rejected and the patient was treated for cardiogenic pulmonary edema and improved considerably. Had she continued to deteriorate, I would have favored an empirical trial with steroids and had she failed this, might have considered a lung biopsy. This form of care is scientifically acceptable because the therapeutic efficiency of lung biopsy in this situation has not been proved and may in fact be negligible.

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Von Willebrand's Disease: A Clinical and Molecular Enigma

Twelfth Annual Paul M. Aggeler Memorial Lecture

Given October 27, 1981
San Franciso General Hospital Medical Center

RALPH L. NACHMAN, MD, *New York City*

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. WALLERSTEIN:* *This is the 12th year of the Paul M. Aggeler Memorial Lecture. As you can see from the following list of previous Aggeler lecturers, they are all giants in hematology: (1) S. I. Rapaport (1970), (2) C. L. Conley (1971), (3) T. H. Spaet (1972), (4) O. D. Ratnoff (1973), (5) J. G. Pool (1974), (6) D. J. Weatherall (1975), (7) E. Beutler (1976), (8) W. N. Valentine (1977), (9) P. W. Majerus (1978), (10) W. F. Rosse (1979), (11) Y. W. Kan (1980). The 1981 speaker, Dr. Ralph Nachman, fits well into this distinguished group.*

DR. SANDE:† Dr. Nachman is a graduate of Vanderbilt University and served his first year of house training there. He then went to New York where he trained in pathology and medicine at Montefiore and The New York hospitals. He has been at The New York Hospital since as a member of the Department of Medicine. He is Professor of Medicine and Chief of the Division of Hematology-Oncology. Dr. Nachman has made a number of outstanding scientific contributions. He has been in the forefront of investigations of platelet function for many years. His research has emphasized the dissection of the platelet, its proteins, its interaction with serum proteins and its interaction with endothelial cells.

Dr. Nachman is a superb blend of an excellent scientist and an excellent clinician. Having trained at The New York Hospital, I and my house staff colleagues recognized him as a teacher who always brought scientific enthusiasm to the bedside. For those of us interested in the study and practice of medicine, he was an almost perfect role model.

*Ralph O. Wallerstein, MD, Chief, Clinical Hematology Division, Medical Services, San Francisco General Hospital and Medical Center and Clinical Professor of Medicine and of Clinical Pathology and Laboratory Medicine, University of California, San Francisco, and Chairman of the Paul M. Aggeler Memorial Committee.

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ABBREVIATIONS USED IN TEXT

VIII:C = factor VIII coagulant
VIII:RAg = factor VIII-related antigen
VIII:RAg_H = factor VIII-related antigen high molecular weight forms
VIII:RAg_L = factor VIII-related antigen low molecular weight forms
VIII/vWF = factor VIII/von Willebrand factor

I think that you will realize this from his lecture entitled "Von Willebrand's Disease—A Clinical and Molecular Enigma."

DR. NACHMAN:* I knew Paul Aggeler and visited him here at this medical center. Over the years, I felt the importance and significance of Dr. Aggeler in the field in which I am generally categorized, namely as a "clotter."

For this Aggeler Memorial Lecture I will review a clinical entity that is a fascinating problem in clotting and represents the cutting edge of platelet function. Like all interesting problems in medicine, it has dragged us from ignorance to important new vistas of physiologic information. Von Willebrand's disease is one entity about which little is known concerning the basic lesions, but we have come a long way in the past 10 or 12 years. Von Willebrand's disease provides insight into the roles factor VIII plays in the blood clotting system. The factor VIII system is a fascinating, challenging and most provocative area of human physiology; in fact, it may become in the next year or two a major focus of the new molecular genetics. As interferon begins to fade as a popular commercial product, other potential molecular genetic products for use in humans will come into the fore. To me, most interesting among the proteins being looked at is the factor VIII/von Willebrand factor (VIII/vWF) system.

The two major factor VIII deficiency states, classic hemophilia and von Willebrand's disease, have clearly shown the importance of this protein system in hemostasis and blood coagulation. The factor VIII system has two distinct biologic functions that are each related to separate macromolecules and each apparently under separate genetic control. The current dogma illustrating the relationship of the separate molecular components of the factor VIII system is shown in Figure 1. Thus, plasma factor VIII circulates as a complex of two components, each of which has a distinct function—detectable immunologically and biochemically. Table 1 lists the currently defined major characteristics of these separate components.

Recent studies have helped to clarify the cell biology of the relationships of the VIII/vWF molecule. A working model of this relationship is shown in Figure 2. Endothelial cells synthesize VIII/vWF, which mediates the adhesion of circulating platelets to the vascular subendothelium, initiating the early stages of platelet plug formation. Glycoprotein (GP) Ib on the platelet surface is necessary for the platelet VIII/vWF interaction. In vitro, ristocetin leads to the binding of VIII/vWF to the platelet surface, resulting in platelet agglutination in platelet-rich plasma. Ristocetin has thus been used as a test to probe the integrity of the GPIb-factor VIII/von Willebrand factor interaction. The physiologic in vivo analogue of ristocetin is unknown, but it is probable that components of the subendothelium directly modulate the von Willebrand factor-platelet interaction.[1] It is of interest that circulating VIII/vWF does not gain access to the intracellular platelet VIII/vWF pool. Megakaryocytes synthesize intracellular granule VIII/vWF, which is

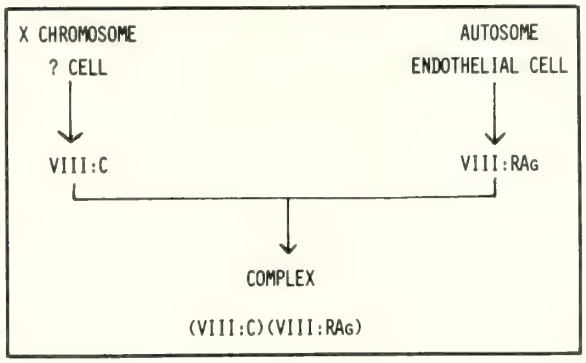

Figure 1.—The factor VIII complex. VIII:C = factor VIII coagulant antihemophilic factor, VIII:RAg = factor VIII-related antigen.

TABLE 1.—*Components of Factor VIII System*

	Major Characteristics
Factor VIII coagulant	Antihemophilic factor. Procoagulant activity = C and procoagulant antigen = VIII:CAg. Antigenic determinants are primarily defined by human antibodies.
Factor VIII-related antigen	Antigenic determinants containing protein and detected by heterologous antibodies. The large polymeric molecule necessary for normal platelet function is the von Willebrand factor (VIII/vWF).

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packaged in platelet alpha granules. The function of intracellular platelet VIII/vWF is not known. Release following platelet membrane perturbation probably saturates the immediate platelet microenvironment and could serve to initiate adhesion to the vascular endothelium.

Physiology of Factor VIII/von Willebrand Factor

Much of our new knowledge of the physiology of VIII/vWF comes from a growing characterization of von Willebrand's disease in humans. Von Willebrand's disease is a congenital hemorrhagic disorder in which an abnormality of VIII/vWF is associated with decreased adhesion of platelets to the subendothelium. The disorder is heterogeneous and several clinical forms of the disease have been recognized. The classic form of the disease is transmitted as an autosomal dominant trait, generally with a mild hemorrhagic syndrome. Two subtypes of the classic form are well recognized. Type 1 von Willebrand's disease is usually associated with a concordant decrease in plasma factor VIII coagulant (VIII:C), factor VIII-related antigen (VIII:RAg) and VIII/vWF. Analysis of VIII:RAg by crossed immunoelectrophoresis reveals a normal polydisperse distribution of molecules.[2,3] Type 2, or *variant,* von Willebrand's disease is associated with discordant decreases in the components of the plasma factor VIII complex, with more pronounced deficit in the VIII/vWF level. Analysis by crossed immunoelectrophoresis of the VIII:RAg present in the plasma of patients with type 2 disease reveals an abnormal pattern with a marked reduction of the larger, slower moving, less anodal molecular forms.[4-6]

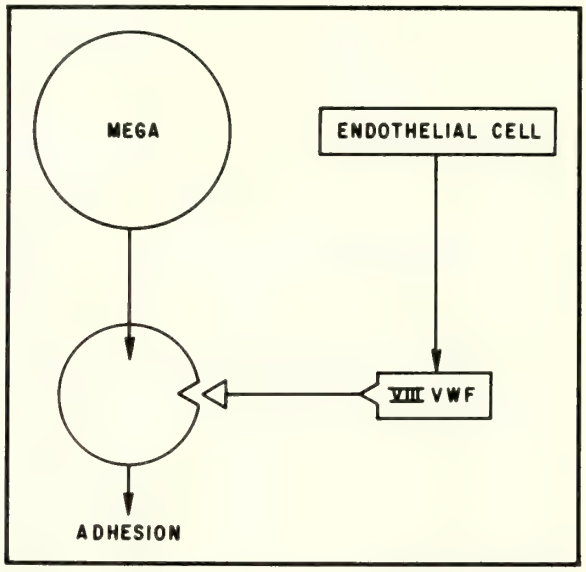

Figure 2.—Cell biology of factor VIII/von Willebrand factor (VIII/vWF) molecule. Endothelial cell synthesizes VIII/vWF, mediating the adhesion of circulating platelets to vascular endothelium and initiating the early stages of platelet plug formation. MEGA = megakaryocyte.

TABLE 2.—*Types of von Willebrand's Disease*

Type	*Hereditary Transmission*	*Major Characteristics*
	Autosomal Dominant	
1	Concordant	↓VIII:RAg, ↓VIII/vWF, ↓VIII:C Normal distribution
2A	Discordant	↓VIII/vWF ↓Cathodal forms
2B	Discordant	↑Ristocetin agglutination ↓Cathodal forms
	Recessive	
1	Heterozygous	NoSx. ↓VIII:RAg
2	Homozygous	Marked ↓VIII:RAg, ↓VIII/vWF, ↓VIII:C ↓Cathodal forms

Abbreviations: RAg = factor VIII-related antigen, VIII/vWF = factor VIII/von Willebrand factor molecule, VIII:C = factor VIII coagulant antihemophilic factor, ↓ = decrease, ↑ = increase and NoSx = no symptoms.

A new subtype of the variant form (type 2B) has been described.[7] This clinical group shows the type 2 abnormal pattern on crossed immunoelectrophoresis but is characterized by enhanced ristocetin-induced platelet agglutination compared with normal platelet agglutination. Variant type 2A von Willebrand's disease is characterized by decreased ristocetin-induced platelet agglutination. A relatively rare form of von Willebrand's disease is apparently transmitted as a recessive trait and is associated with a severe hemorrhagic syndrome in homozygous patients. Trace amounts of VIII:RAg in these patients also lack the larger less anodal molecular forms.[8] The various types of von Willebrand's diseases are shown in Table 2.

The molecular basis for the heterogeneous nature of von Willebrand's disease is not well understood. The disorder has been assumed to be associated with either a quantitative or a qualitative abnormality of the VIII/vWF protein (or both). The VIII/vWF complex is necessary for normal platelet function and is measured in vivo by the bleeding time and in vitro by the amount of ristocetin-induced platelet agglutination. It is the functional attribute of VIII:RAg.[9] Several studies have suggested that the factor VIII:RAg molecules in type 2 variant von Willebrand's disease may be qualitatively abnormal analogous to hemo-

globinopathies.[5,6,10] Recent studies suggest that the abnormality in von Willebrand's disease is due to an abnormal distribution of polymeric forms of VIII:RAg.[11]

To determine whether or not VIII:RAg in von Willebrand's disease is structurally abnormal, the VIII:RAg molecules in normal-pooled plasma, in plasma from four patients with type 1 von Willebrand's disease and in plasma from one patient with type 2A von Willebrand's disease have been isolated, iodinated and subjected to tryptic digestion, and the radioactive peptide maps have been compared.

Experimental Results

The electrophoretic distribution of the VIII:RAg in the patients' plasma used for these studies is shown in Figure 3. All of the patients with the concordant type 1 von Willebrand's disease showed similar electrophoretic patterns. To characterize the different types of VIII:RAg in the patients' plasma, the proteins were immunoisolated by the method of Kessler.[12] The VIII:RAg in normal and von Willebrand's plasma was isolated using monospecific rabbit anti-VIII:RAg bound to killed staphylococci (which bind to the C fragment of immunoglobulins) and analyzed by a sodium dodecyl sulfate (SDS)/polyacrylamide gel system that clearly differentiated VIII:RAg from fibronectin. The VIII:RAg bands in the immunoprecipitates from normal and von Willebrand's plasma barely entered the gels and moved to the same position as a purified nonimmunoprecipitated VIII:RAg derived from normal pooled plasma (Figure 4). When removed from unstained gels and reduced with dithiothreitol, the normal and von Willebrand's VIII:RAg bands moved into the gels with apparent molecular weights of 200,000. The major lower molecular weight bands in the SDS gels of the normal and von Willebrand's VIII:RAg immunoprecipitates comigrated with immunoglobulin. To determine whether or not the other minor contaminants were related immunologically to the VIII:RAg system,

Figure 4.—Immunoisolation of VIII:RAg on unreduced SDS gels. **A,** chromatographed normal plasma VIII:RAg; **B,** type 1 von Willebrand's disease VIII:RAg; **C,** type 2A von Willebrand's disease VIII:RAg; **D,** immunoisolated normal plasma VIII:RAg. VIII:RAg = factor VIII-related antigen. (Reproduced with permission of publisher from Nachman RL et al: *Proceedings of the National Academy of Sciences, U.S.A.,* 1980; 77:6832-6836.)

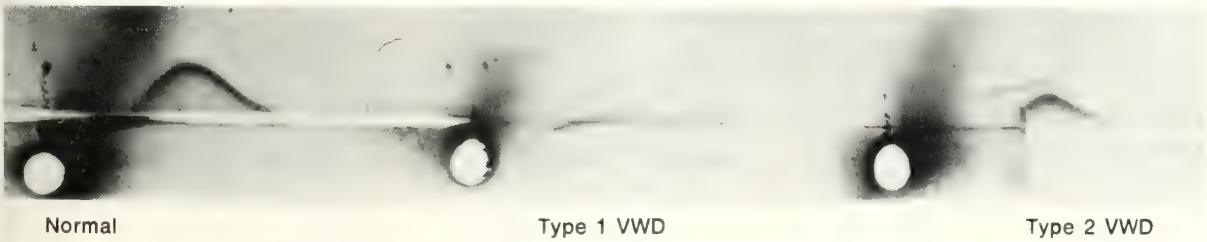

Figure 3.—Crossed immunoelectrophoresis of pooled normal plasma, plasma from type 1 von Willebrand's disease (VWD), and plasma from type 2A VWD. (Reproduced with permission of publisher from Nachman RL et al: Structural analysis of factor VIII antigen in von Willebrand's disease. *Proceedings of the National Academy of Sciences, U.S.A.* 1980; 77:6832-6836.

two-dimensional immunoelectrophoresis of the normal and von Willebrand's factor VIII immunoprecipitates was performed. Only the high molecular weight band comigrating with the purified plasma VIII:RAg marker clearly reacted with the monospecific anti-VIII:RAg. No immunoprecipitate was detected when fibronectin was analyzed in the same system.

To determine the structural relationship among the several VIII:RAg preparations, the fixed and stained reduced proteins in the SDS gels were removed, radioiodinated and subjected to tryptic digestion.[13] Autoradiographs of representative two-dimensional peptide maps are shown in Figure 5. The peptide maps of VIII:RAg immunoisolated from normal-pooled plasma, type 1 von Willebrand's disease plasma and type 2A von Willebrand's disease plasma were remarkably similar. No unique normal VIII:RAg or von Willebrand's VIII:RAg peptides were detected. All of the peptide spots present in normal VIII:RAg were present in types 1 and 2A von Willebrand's VIII:RAg, though the relative density of some of the peptide spots varied. All of the peptides present in the type 1 protein were identified in the type 2A protein. Peptide maps of VIII:RAg in the different patients with type 1 von Willebrand's disease were identical. Peptide maps of equal mixtures of normal and von Willebrand's plasma VIII:RAg and mixtures of types 1 and 2 von Willebrand's VIII:RAg revealed overlapping peptide patterns. The peptide maps of chromatographically purified normal plasma VIII:RAg and immunoisolated plasma VIII:RAg were identical.

Discussion

The plasma proteins analyzed in these studies were quite large in the reduced state, with molecular weights of 200,000. It is not unlikely that a single amino acid substitution could have been missed by this technique, particularly if present in a relatively lightly labeled peptide. The possibility has also to be considered that a mutant tyrosine-free (and therefore unlabeled) peptide would be undetected by this method. Despite these reservations the remarkable structural similarity of the isolated proteins from these unrelated pa-

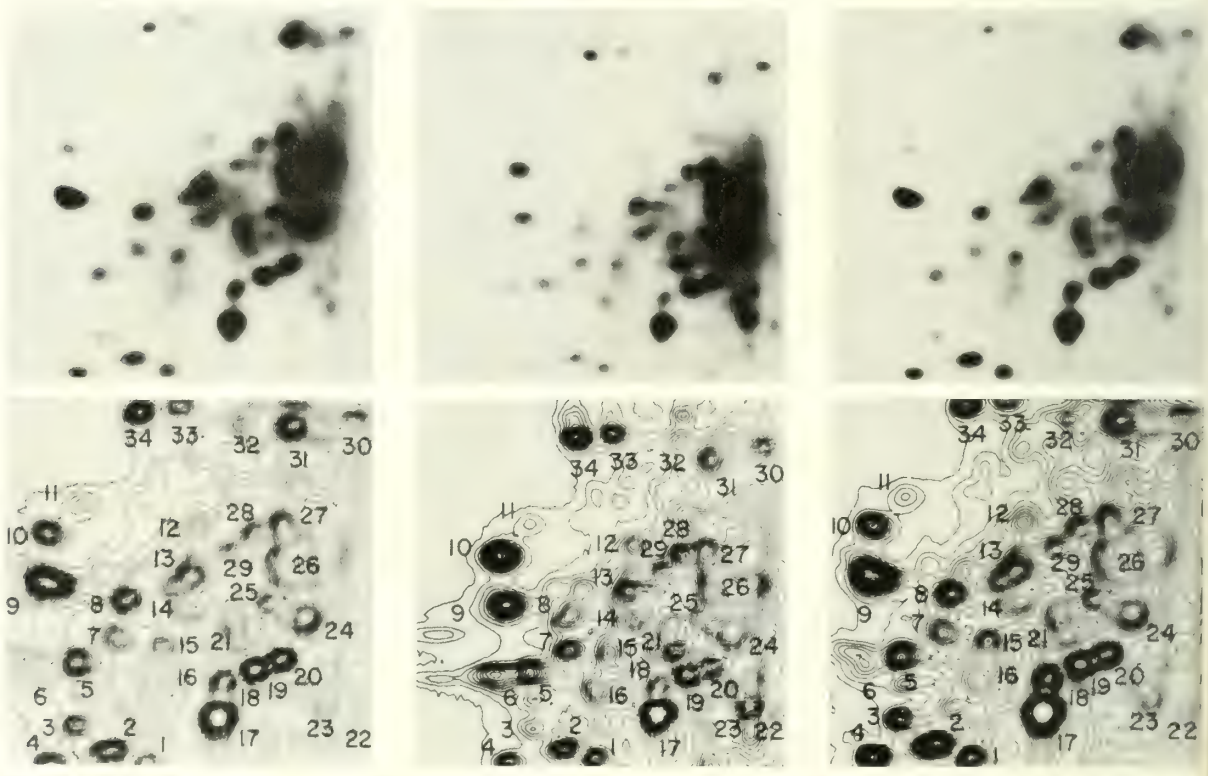

Figure 5.—Autoradiographs of two-dimensional maps of tryptic pepsin labeled with iodine 125(^{125}I) showing immunoisolated VIII:RAg from normal plasma, Type 1 von Willebrand's disease (VWD) and Type 2 VWD. Below each radiograph is shown the corresponding computer-plotted density contour map. Arbitrary peptide numbers have been used for comparison. RAg = factor VIII-related antigen. (Reproduced with permission of publisher from Nachman RL et al: *Proceedings of the National Academy of Sciences, U.S.A.* 1980; 77:6832-6836.)

Figure 6.—Crossed immunoelectrophoresis of endothelial cell postculture medium VIII:RAg **(left)** and intracellular endothelial VIII:RAg **(right).** VIII:RAg = factor VIII-related antigen.

tients raises the strong possibility that the plasma VIII:RAg molecules in types 1 and 2 von Willebrand's disease are identical with normal plasma VIII:RAg. The observations suggest that von Willebrand's disease may be primarily a disorder of quantitative rather than qualitative aberration in circulating VIII:RAg molecules.

It is not surprising that VIII:RAg in the plasma of patients with type 1 von Willebrand's disease is identical to normal VIII:RAg. This might be predicted from the crossed immunoelectrophoretic pattern where the abnormality appears to be primarily quantitative in nature, that is, a normal distribution of lesser amounts of the multiple molecular forms. The apparent identity of the VIII:RAg in variant von Willebrand's disease plasma with normal VIII:RAg is further substantiated by the recent studies showing that the abnormality in von Willebrand's disease reflects an abnormal distribution of polymeric forms.[11,14] The distribution of the VIII:RAg polymers is slightly different in the two subtypes of variant von Willebrand's disease (types 2A and 2B). Patients with type 2B von Willebrand's disease and an enhanced ristocetin response may be a particularly informative group to analyze for structural abnormalities.[11] With highly sensitive immunologic techniques, it is now possible to detect small amounts of VIII:RAg in the severe recessive form of von Willebrand's disease.[8] This heterogeneous group may well contain subsets of patients with amino acid-substituted VIII:RAg molecules.

The possibility has to be considered that the carbohydrate residues on VIII:RAg may be important in determining von Willebrand's factor function. Sialic acid removal may critically influence the ability of the protein to support ristocetin-induced platelet agglutination.[15] Oxidation of the penultimate galactose of VIII:RAg reduces the von Willebrand's factor activity.[16] Modification of the carbohydrate residue impairs binding of VIII/vWF to platelet surfaces.[17]

Our observations on the apparent identical structure of VIII:RAg in two different types of von Willebrand's disease raise questions regarding the normal physiologic relationships in the factor VIII system. The VIII:RAg in normal plasma is heterogeneous and exists as a polydisperse series of molecular forms of different molecular weights.[14,18-20] The basis for this molecular heterogeneity is not fully understood. The molecular dispersity may represent polymeric subunit combinations.[20] Ekert and Chavin[21] suggested that VIII:RAg molecules exist in polymeric forms that spontaneously dissociate and exist in equilibrium with a pool of partially dissociated subunits. The fact that the low and high molecular weight forms appear to be indistinguishable on the basis of primary structure as illustrated in our studies strengthens the possibility that these molecular forms are composed of different-sized multimers of identical subunits. The carbohydrate composition of the different-sized multimers remains to be determined. The multimeric composition of the VIII:RAg present in types 2A and 2B variant von Willebrand's disease supports this premise.[11]

Transfusion experiments using radiolabeled VIII:RAg in human volunteers demonstrate that the higher molecular weight forms disappear faster.[22] These observations raise the intriguing possibility that there may be a continuous conversion of the high molecular weight forms (possessing von Willebrand factor activity) into lower molecular forms (lacking von Willebrand activity).[23] Similar observations after transfusion in patients with von Willebrand's disease suggest in

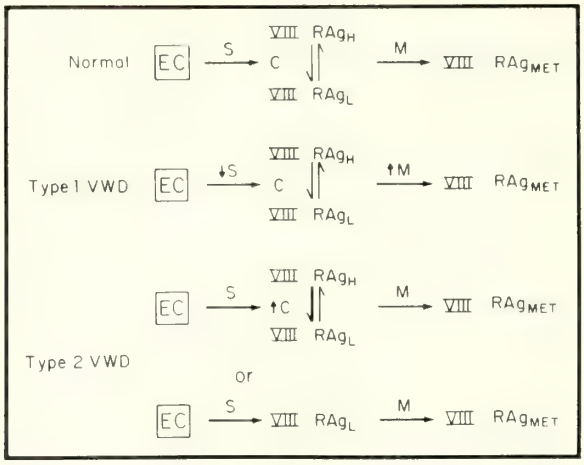

Figure 7.—Hypothetic scheme for relationship of VIII:RAg forms in normal and von Willebrand's disease. VWD = von Willebrand's disease; EC = epithelial cell; VIII:RAg_H = factor VIII-related antigen high molecular weight forms; VIII:RAg_L = factor VIII-related antigen low molecular weight forms; VIII:RAg_{Met} = metabolized products; S = syntheses; C = conversion; M = catabolic rate. (Reproduced with permission of publisher, modified from Nachman RL et al: *Proceedings of the National Academy of Sciences, U.S.A.*, 1980; 77:6832-6836.)

vivo conversion of high molecular weight VIII:RAg into lower molecular weight VIII:RAg.

Comparison of VIII:RAg isolated from endothelial cell postculture medium and intracellular nonsecreted endothelial cell VIII:RAg also suggests the possibility of conversion of intracellular low molecular weight forms into higher extracellular molecular weight forms extracellularly (Figure 6). This raises the possibility of an endothelial cell polymerizing activity that is necessary for the full expression of VIII:vWF function.

The mechanisms that regulate the conversion of slower moving, higher molecular weight forms of VIII:RAg into faster moving, lower molecular weight forms are not understood at present. The quantitative character of the abnormalities in these two common types of von Willebrand's disease suggests that the altered synthetic or catabolic rates and compartmental shifts of normal population subsets of molecules might be the basis for the clinical disorder. A working hypothesis for these potential relationships is shown in Figure 7. Under normal circumstances, endothelial cells synthesize and release into the plasma a polydisperse population of VIII:RAg molecules that contains a significant percentage of higher molecular weight forms. The factor VIII-related antigen high molecular weight forms (VIII:RAg_H, cathodal) are converted in the circulation to factor VIII-related antigen low molecular weight forms (VIII:RAg_L, anodal).[22] The hypothesis allows for the possible physiologic rearrangement of VIII:RAg_L to form VIII:RAg_H. The resulting polydisperse population is then catabolized.

In type 1 von Willebrand's disease, there is primarily an altered synthetic or catabolic rate such that there are low levels of circulating plasma VIII:RAg molecules. However, the conversion rate of high molecular weight forms is normal, and thus the molecules that are present are normally polydispersed. In type 2A von Willebrand's disease, the primary abnormality could be reflected in an accelerated conversion rate of VIII:RAg_H to VIII:RAg_L or there might be a direct defect in endothelial synthesis leading only to VIII:RAg_L release. It is of interest that there appears to be an absolute increase in the smaller molecular weight multimers in the plasma of patients with type 2A variant von Willebrand's disease.[11,14] This is compatible with an accelerated rate of conversion of high molecular weight forms to low molecular weight forms. In addition, the intraplatelet VIII:RAg in patients with type 2A von Willebrand's disease has greater amounts of the larger molecular weight multimers than the plasma. This suggests that intracellular sequestration may protect the multimeric VIII:RAg complex from rapid conversion of high molecular weight forms to low molecular weight forms.

The hypothetic model raised by these considerations does not preclude the possibility that von Willebrand's disease is a heterogeneous disorder that in some circumstances may be associated with qualitatively defective molecules.

REFERENCES

1. Sakariassen KS, Bolhuis PA, Sixma JJ: Human blood platelet adhesion to artery subendothelium is mediated by factor VIII-von Willebrand factor bound to the subendothelium. Nature 1979; 279:636-638

2. Italian Working Group: Spectrum of von Willebrand's disease: A study of 100 cases. Br J Haematol 1977; 35:101-112

3 Shoa'i I, Lavergne JM, Ardaillous N, et al: Heterogeneity of von Willebrand's disease—Study of 40 Iranian cases. Br J Haematol 1977; 37:67-83

4. Kernoff PBA, Gruson R, Rizza CR: A variant of factor VIII related antigen. Br J Haematol 1974; 26:435-440

5. Peake IR, Bloom AL, Giddings JC: Inherited variants of factor VIII-related protein in von Willebrand's disease. N Engl J Med 1974; 291:113-117

6. Gralnick H, Sultan Y, Coller BS: Von Willebrand's disease—Combined qualitative and quantitative abnormalities. N Engl J Med 1977; 296:1024-1030

7. Rugger ZM, Pareti FI, Manucci PM, et al: Heightened interaction between platelets and factor VIII/von Willebrand's factor or a new subtype of von Willebrand's disease. N Engl J Med 1980; 302:1047-1051

8. Zimmerman TS, Abilgaard CF, Meyer D: The factor VIII abnormalities in severe von Willebrand's disease. N Engl J Med 1979; 301:1307-1310

9. Weiss HJ, Hoyer LW, Rickles FR, et al: Quantitative assay of a plasma factor deficient in von Willebrand's disease that is necessary for platelet aggregation—Relationship to factor VIII procoagulant activity and antigen content. J Clin Invest 1973 52:2708-2716

10. Sultan Y, Simeon J, Caen JP: Electrophoretic heterogeneity or normal factor VIII/Von Willebrand protein, and abnormal electrophoretic mobility in patients with Von Willebrand's disease. J Lab Clin Med 1976 Feb; 87:185-194

11. Ruggeri ZM, Zimmerman TS: Variant von Willebrand's disease—Characterization of two subtypes by analysis of multimeric composition of factor VIII/von Willebrand factor in plasma and platelets. J Clin Invest 1980; 65:1318-1325

12. Kessler SW: Rapid isolation of antigens from cells with a staphylococcal protein A-antibody absorbent: Parameters of the interaction of antibody-antigen complexes with protein A. J Immunol 1975 Dec; 115:1617-1624

13. Elder JH, Pickett RA II, Hampton J, et al: Radioiodination of proteins in single polyacrylamide gel slices—Tryptic peptide analysis of all the major members of complex multicomponent systems using microgram quantities of total proteins. J Biol Chem 1977; 252:6510-6515

14. Meyer D, Obert B, Pietu G, et al: Multimeric structure of factor VIII/von Willebrand factor in von Willebrand's disease. J Lab Clin Med 1980 Apr; 95:590-602

15. Sodetz JM, Pizzo SV, McKee P: Relationship of sialic acid to function and in vivo survival of human factor VIII/von Willebrand factor protein. J Biol Chem 1977; 252:5538-5546

16. Gralnick HR: Factor VIII/von Willebrand factor protein—Galactose a cryptic determinant of von Willebrand factor activity. J Clin Invest 1978 Aug; 62:496-499

17. Kao K-J, Pizzo SV, McKee P: Factor VIII/von Willebrand protein—Modification of its carbohydrate causes reduced binding to platelets. J Biol Chem 1980; 255:10134-10139

18. Zimmerman TS, Roberts J, Edgington TS: Factor VIII-related antigen: Multiple molecular forms in human plasma. Proc Natl Acad Sci USA 1975; 72:5121-5125

19. Mourik JA van, Bouma BN, LaBruyère FT, et al: Factor VIII, a series of homologous oligomers and a complex of two proteins. Thromb Res 1974 Jan; 4:155-164

20. Mourik JA van, Bolhuis PA: Dispersity of human factor VIII-von Willebrand factor. Thromb Res 1978 Jul; 13:15-24

21. Ekert H, Chavin SI: Changes in electrophoretic mobility of human factor VIII-related antigen: Evidence for subunit structure. Br J Haematol 1977; 36:271-279

22. Over J, Sixma JJ, Doucet-de Briüne MH, et al: Survival of ^{125}iodine-labeled Factor VIII in normals and patients with classic hemophilia—Observations on the heterogeneity of human Factor VIII. J Clin Invest 1978 Aug; 62:223-234

23. Over J, Bouma BN, Sixma JJ, et al: Heterogeneity of human factor VIII—III. Transition between forms of factor VIII present in cryoprecipitate and in cryosupernatant plasma. J Lab Clin Med 1980 Mar; 95:323-334

Important Advances in Clinical Medicine

Epitomes of Progress—Pediatrics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in pediatrics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Undescended Testes—When to Treat

NORMAL TESTES, which develop from the ventral border of the urogenital ridge, descend retroperitoneally and traverse the inguinal canal to reside in the base of the scrotum. The left testis descends earlier than the right and is normally a bit lower. When testicular descent is incomplete, there is risk of decreased spermatogenesis and malignant change in the testes.

Basic to therapy is the differentiation between incomplete descent of a testis and one that is retractile. If a testis can be manipulated into the scrotum or is in the scrotum part of the time, therapy is unnecessary. In some boys the cremaster reflex is more active than usual, causing the testes to reside in the inguinal canal most of the time. When a boy approaches puberty, a retractile testis will stay in the scrotum.

If a testis cannot be manipulated into the scrotum, it is abnormal and should be treated. Medical and surgical therapy are both currently acceptable and in some cases both may be used.

Approximately 30 percent of premature infants, 3 percent of full-term infants and 0.3 percent of adults will have an undescended testis. These statistics indicate that testicular descent does occur in some patients after birth.

At approximately two years of age, patients with an undescended testis will have less than normal spermatogonia count and the tubular diameters of the testes will be below normal. Unless the patient has an associated hernia that is troublesome, treatment is best carried out between the ages of two and four years.

Medical therapy (chorionic gonadotropin) is more effective in patients who have bilateral undescended testes than in those who have a unilateral undescended testis. Successful testicular descent occurs in approximately 30 percent of patients with bilateral undescended testes and approximately 15 percent of patients with unilateral undescended testis. The side effects of therapy are enlargement of the phallus and rugosity of the scrotum. Many parents refuse medical therapy for their sons when informed of the side effects. If a testis remains undescended at the end of the therapy, a surgical procedure should be recommended.

When surgical therapy is advised primarily or after failure of medical therapy, orchidopexy, using the technique of creating a scrotal pouch between the scrotal skin and the tunica dartos, appears to be the best of the current operations. This procedure can be carried out in an outpatient surgical unit and requires no external fixation.

Surgical therapy should be recommended if a testis has not descended by 2 years of age.

Malignant lesions of the testis are 40 times more common in patients with undescended testes than in patients whose testes have descended normally. Medical or surgical therapy does not affect the frequency of occurrence of malignant tumors; however, the diagnosis can be made earlier if the testis is in the scrotum where the tumor can be palpated. A malignant lesion will develop in approximately 1 in 1,100 patients with undescended testis, most commonly in the third decade of life. Spermatogenesis is increased by orchidopexy; however, the average sperm count in a man who has had undescended testis will be lower than normal. There appears to be an inherent abnormality in undescended testes that is not altered by medical or surgical descent.

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REFERENCES

Woolley MM: Cryptorchidism, *In* Ravitch MM, et al (Ed): Pediatric Surgery, 3rd Ed. Chicago, Year Book Medical Publishers, 1979, pp 1399-1410

Woolley MM: Orchidopexy. Surg Techniques Illustrated 1978 Autumn; 3(4):69-80

Treatment of Metatarsus Adductus in Infants

METATARSUS ADDUCTUS or, more properly, metatarsus varus is a medial deviation of the forefoot, sometimes referred to as "skew foot" or "one third of a club foot." It generally refers to a condition in which the forefoot is supinated and adducted, while the hindfoot is in a slight valgus position.

The incidence as reported by Wynne-Davies is 1 per 1,000 live births, with afflicted females outnumbering afflicted males 4 to 3. These figures may be low as they were obtained from hospital records, and this condition does not always require hospital level attention. Metatarsus varus is generally quoted as being ten times more frequent than club foot, though the incidence of club foot is also reported as 1 per 1,000 live births from the same Wynne-Davies data. There is no clear pattern of inheritance and there is no relation of incidence to intrauterine environmental factors.

Metatarsus varus may present clinically three ways—as a stiff or fixed adduction, supple or "hooked" forefoot or dynamic forefoot adduction.

In the stiff variety, always present at birth, the forefoot is extremely adducted, the foot imprint shows a high arch, the great toe is medially deviated, the medial foot is creased, the lateral foot shows a prominent fifth metatarsal base and the forefoot is not passively correctable to a neutral axis. Manual stroking of the lateral aspect of the foot while firmly holding the heel does not elicit a peroneal muscle reflex, which corrects the forefoot to neutral.

The flexible, or supple, metatarsus varus, with varying degrees of the above deformities, is passively overcorrectable; manual stroking of the lateral foot elicits spontaneous correction to neutral. This type is also usually present at birth and usually corrects spontaneously. This explains such reports as Rushforth's in which 86 percent of 130 patients were found to have normal feet without treatment at an average follow-up of 7 years. Ponseti and Becker noted that only 11.6 percent of 379 patients needed casting. A few flexible cases may stiffen and require treatment later.

The dynamic forefoot adduction group may not have a concave varus foot at rest, but will have varus forefoot on weight-bearing. In these feet, dynamic deforming forces, such as an overactive abductor hallucis or an anomalous posterior tibial insertion, may be the cause. This explains the pediatrician's shock at seeming to miss some severe adducted forefeet until the children begin to walk. These usually spontaneously improve, but may resist casting or passive correction (since the deformity is dynamic) and may need surgical muscle release if persistent into the third or fourth year.

Treatment of stiff metatarsus varus with serial casting is warranted as soon as the condition is recognized. Early orthopedic referral is prudent. All other forms of flexible metatarsus varus will usually correct spontaneously during the first three years of life. Parental stretching is not effective in a stiff foot and unnecessary in a supple foot, and, if improperly applied, may produce a "Z" foot.

There is agreement that reverse-last shoes will not correct the stiff foot, and are unnecessary in the spontaneously self-correcting flexible deformity. Shoes may be of temporary assistance after casting for maintenance, though it is generally agreed that mild overcorrection is the best endpoint in casting.

The Denis-Browne bar with shoes should be reserved for varus deformity that is accompanied by severe internal tibial torsion, and probably only after 18 months to 2 years of age. the bar can actually cause an externally rotated or valgus

hindfoot without correction of the forefoot adduction, resulting in a Z or so-called serpentine foot.

If stiffness persists beyond age 3 or 4 years, surgical soft tissue midfoot release or bony metatarsal osteotomy may become necessary.

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REFERENCES

Bleck EE: The shoeing of children: Sham or science? Dev Med Child Neurol 1971 Apr; 13:188-195

Ponseti IV, Becker JR: Congenital metatarsus adductus: The results of treatment. J Bone Joint Surg 1966 Jun; 48:702-711

Rushforth GF: The natural history of hooked forefoot. J Bone Joint Surg 1978 Nov; 60-B:530-532

Wynne-Davies R: Family studies and the cause of congenital club foot—talipes equinovarus, talipes calcaneo-valgus and metatarsus varus. J Bone Joint Surg 1964 Aug; 46-B:445-463

Antimicrobial Therapy for Acute Otitis Media in Children

THE PREFERRED ANTIMICROBIAL agent for a child with acute otitis media must be active against *Streptococcus pneumoniae* and *Hemophilus influenzae*. Group A streptococcus and *Staphylococcus aureus* are infrequent causes of acute otitis media and need not be considered in initial therapeutic decisions. Gram-negative enteric bacilli must be considered when otitis media occurs in newborn infants, in patients with depressed immune response and those with suppurative complications of chronic otitis media.

Most antimicrobial agents effective in the treatment of otitis media can be found in significant concentrations in middle ear fluid. After administration of the agent, antimicrobial activity occurs promptly in middle ear fluid and duration is approximately the same as in serum.

Usual dosage schedules of ampicillin, amoxicillin trihydrate, cefaclor and trimethoprim-sulfamethoxazole (TMP-SMZ) produce concentrations of antimicrobial activity in middle ear fluid that are sufficient to inhibit *Streptococcus pneumoniae* and most strains of *H influenzae*. Concentrations achieved in middle ear fluid by penicillin V, the erythromycins and clindamycin hydrochloride are sufficient to inhibit *S pneumoniae* but are not adequate to inhibit most strains of *H influenzae*.

Amoxicillin or ampicillin are still the drugs of choice for initial treatment of otitis media because they are active both in vitro and in vivo against *S pneumoniae* and *H influenzae* and are less expensive than alternative regimens. The current incidence of ampicillin-resistant *H influenzae* is low, approximately 3 percent to 8 percent of cases of otitis media, and does not require a change in initial therapy. Other drugs that are satisfactory include TMP-SMZ, cefaclor and combinations of a sulfonamide and penicillin G, penicillin V, erythromycin or clindamycin. For the child who is allergic to penicillin, TMP-SMZ, cefaclor or the combination of erythromycin or clindamycin and a sulfonamide provide equivalent antimicrobial coverage.

With appropriate antimicrobial therapy, most children with acute otitis media due to one of the common bacterial pathogens feel considerably better within 48 to 72 hours. If symptoms have not lessened, the patient should be reexamined. Toxicity with persistent or recurrent fever or otalgia should prompt tympanocentesis to identify the causative organism; the appropriate antimicrobial agent may then be chosen based on results of culture of middle ear fluid. If signs persist but the child is not toxic and aspiration is not performed, the initial antimicrobial regimen should be changed to one that is effective for uncommon organisms, including β-lactamase-producing *H influenzae*. Recent studies indicate that if ampicillin or amoxicillin was initially given, then administration of TMP-SMZ, erythromycin-sulfisoxazole or cefaclor is usually successful. TMP-SMZ is probably ineffective when group A β-hemolytic streptococcus or *Staphylococcus aureus* is the causative organism.

The bacteriology of middle ear infection in children who have recurrent episodes of acute otitis media is similar to that for first episodes; the predominant pathogens are *Streptococcus pneumoniae* and nontypable strains of *H influenzae*. Thus, a child with a recurrent episode of otitis media should be treated initially with the same antimicrobial regimen as a child with a first episode of middle ear infection.

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REFERENCES

Ginsburg CM, McCracken GH Jr, Nelson JD: Pharmacology of oral antibiotics used for treatment of otitis media and tonsillopharyngitis in infants and children. Ann Otol Rhinol Laryngol (Suppl 84) 1981 May-Jun; 80:37-43

Klein JO: Microbiology of otitis media. Ann Otol Rhinol Laryngol (Suppl) 1980 May-Jun; 89(3 Pt 2 Suppl 68):98-101

Schwartz RH, Schwartz DM: Acute otitis media: Diagnosis and drug therapy. Drugs 1980 Feb; 19:107-118

Laboratory Aids in the Diagnosis of Testicular Torsion

TESTICULAR TORSION results in the sudden devascularization of the testicle. In most cases this condition must be differentiated from either epididymitis or torsion of the testicular appendages.

Since epididymitis is almost always associated

with prostatitis, probably the easiest and most successful laboratory aid in the differential diagnosis of an acutely swollen scrotum is urine examination. If no leukocytes are seen in the first part of the voided urine specimen, the diagnosis of testicular torsion should be considered and plans made for immediate surgical exploration. If the diagnosis is in doubt, however, a Doppler ultrasonogram or a radioisotope testicular scan, or both, may be used for evaluating the blood flow to the testis. With either epididymitis or torsion of the testicular appendages, one would not expect to detect any impairment of perfusion of blood through the testes.

The Doppler ultrasonic stethoscope is a pocket-size instrument capable of picking up the vascular pulsations to the testis, the intensity of which is proportional to the magnitude of the blood flow. A sonographic recording can be obtained by connecting the Doppler stethoscope to an electrocardiogram machine or some other appropriate recording device. This means of evaluating testicular blood flow is simple, immediate and reasonably reliable.

Testicular scanning using sodium pertechnetate Tc 99m has also become an accepted technique for assessing testicular blood flow in a patient with acutely swollen scrotum. Although a recent comparative study of these two methods revealed a better correlation of the testicular scan than of the Doppler ultrasonogram with the surgical findings, a scanning camera is not available in most medical offices or emergency rooms.

It must be emphasized that testicular torsion is an emergency situation in which the diagnosis must be made rapidly and detorsion accomplished promptly. The lack of leukocytes in the urine in a male of any *age* who has a tender swollen scrotum should alert the physician to the most likely diagnosis of testicular torsion. To confirm vascular impairment to the testis, the use of either a Doppler ultrasonic stethoscope or a radioisotope testicular scan can be most helpful. Yet, though laboratory evidence of an avascular testis can be reassuring to the clinician, such evidence does little for the testis if detorsion has been delayed pending results of these studies. Only by immediate exploration and reestablishment of the testicular blood flow by detorsion can a satisfactory rate of testicular salvage be obtained.

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REFERENCES

Cass AS, Cass BP, Veeraraghavan K: Immediate exploration of the unilateral acute scrotum in young male subjects. J Urol 1980 Dec; 124:829-832

Hahn LC, Nadel NS, Gitter MH, et al: Testicular scanning: A new modality for the preoperative diagnosis of testicular torsion. J Urol 1975 Jan; 113:60-62

Levy BJ: The diagnosis of torsion of the testicle using the Doppler ultrasonic stethoscope. J Urol 1975 Jan; 113:63-65

Rodriguez DD, Rodriguez WC, Rivera JJ, et al: Doppler ultrasound versus testicular scanning in the evaluation of the acute scrotum. J Urol 1981 Mar; 125:343-346

The Effect of DES on Male Offspring

VARIOUS COMPLICATIONS of pregnancy, notably threatened abortion, were commonly treated with diethylstilbestrol (DES) during the 1940's through the 1960's. Prenatal exposure to DES became a cause for concern in 1971 when accumulated evidence linked clear-cell adenocarcinoma of the vagina and vaginal adenosis with the administration of DES during pregnancy to the mothers of the affected young women. Later, concern arose regarding hazards of transplacental DES on the developing male fetus.

Follow-up comparison 25 years or later on subjects involved in a double-blind study of the efficacy of DES in preventing untoward effects of pregnancy showed DES-exposed males to have a greater prevalence of epididymal cysts, hypoplastic testes or both. Of 308 males exposed to DES, 31.5 percent had epididymal cysts, hypoplastic testes or both, as compared with 7.8 percent of 307 placebo-exposed controls. Of 26 DES-exposed males with testicular hypoplasia, 17 had a history of cryptorchidism, while only 1 of 6 placebo-exposed males with testicular hypoplasia had a history of testicular maldescent. Analysis of semen of 134 males exposed to DES showed severe pathologic changes in 18 percent compared with 8 percent of 87 male controls. This finding suggests that DES exposure in utero may have an effect on male fertility.

Although there is no control study showing an increased incidence of malignant tumors among DES-exposed men, one must keep in mind the increased risk of testicular carcinoma in testes that are or were cryptorchid. Testicular carcinoma has been reported in three men who had a history of exposure to DES in utero and of cryptorchidism. There has as yet been no report of carcinoma of the prostatic utricle in men exposed to DES in utero. The prostatic utricle, the müllerian duct remnant that is homologous to the female vagina, has been found to be the site of carcinoma in older men.

In summary, administration of DES during preg-

nancy appears to be followed by male genital tract abnormalities that are both structural (epididymal cysts, hypoplastic testes and cryptorchidism) and functional (abnormal semen). Due to prolonged latency in expression of DES effects, it will probably be another decade or more before the question of potential malignancy in men exposed to DES in utero is answered. Additional follow-up will also give insight into the probability of subnormal fertility in males exposed to DES in utero.

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REFERENCES

Driscoll SG, Taylor SH: Effects of prenatal maternal estrogen on the male urogenital system. Obstet Gynecol 1980 Nov; 56: 537-542

Gill WB, Schumacher GF, Bibbo M, et al: Association of diethylstilbestrol exposure in utero with cryptorchidism, testicular hypoplasia and semen abnormalities. J Urol 1979 Jul; 122:36-39

Whitehead ED, Leiter E: Genital abnormalities and abnormal semen analyses in male patients exposed to diethylstilbestrol in utero. J Urol 1981 Jan; 125:47-50

Treatment of Disseminated Herpes Infections in Newborns and Infants

HERPES SIMPLEX VIRUS (HSV) infection of the newborn frequently results in fatal or otherwise devastating disease. The virus is usually transmitted during delivery from the maternal genital tract infected with herpes simplex virus, with HSV type 2 accounting for 85 percent of newborn HSV infections. Clinical signs appear most often between the first and second weeks of life, but may be present at birth or may not be found until the infant is a month of age. Untreated, 50 percent of all newborns with HSV infections will die and half of the survivors will be neurologically abnormal at 2 years of age. Infants with central nervous system (CNS) or disseminated disease have fatal infections in 75 percent of cases. Recently, vidarabine (adenine arabinoside) therapy administered intravenously has been shown to improve the outcome of newborns with HSV infections, mortality being significantly reduced in babies with CNS and disseminated disease from 74 percent to 38 percent. Disseminated HSV disease, however, shows less of a decrease, from 85 percent to 57 percent mortality. Most important with localized CNS disease, mortality was not only reduced from 50 percent to 10 percent, but 50 percent of infected babies were neurologically normal at 2 years with treatment.

These recent findings of the National Institute of Allergy and Infectious Disease (NIAID) Collaborative Antiviral Study Group indicate that vidarabine therapy significantly improves the outcome of newborns with HSV infections. Acyclovir (ACV, 9-(2-hydroxyethoxymethyl) guanine) is a new antiviral agent that has been shown to be effective against certain herpesvirus infections both in vitro and more recently in human studies. The substantially greater solubility of ACV, combined with its high therapeutic index and low toxicity, offers potentially important advantages over vidarabine. The NIAID is currently conducting a randomized study comparing the effect of vidarabine with ACV. The results of this study will not be known for at least two years.

Until the study is completed, a physician who suspects a case of neonatal herpes should admit the child to an intensive care hospital setting where facilities are available for caring for a critically ill infant. When possible the infant should be treated in a regional center involved in the NIAID study for management and random assignment to either ACV or vidarabine therapy. An infant in hospital in a nonstudy center intensive care unit should be treated with vidarabine. If skin vesicles are present or positive herpes cultures are available from any site in the infant, antiviral therapy should be initiated immediately, since 75 percent of infants who have cutaneous HSV will develop CNS disease. Almost 20 percent of newborns with proved HSV will not develop skin vesicles and 5 percent to 10 percent will require brain biopsy for virologic confirmation of HSV infection. Any baby excreting HSV within the first month of life should be considered in mortal danger and treated as outlined above. The prompt institution of therapy will favorably influence the outcome of an infant with proved herpetic infection.

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REFERENCES

Spector SA, Connor JD, Hintz M, et al: Single-dose pharmacokinetics of acyclovir. Antimicrob Agents Chemother 1981 Apr; 19:608-612

Whitley RJ, Nahmias AJ, Soong S-J, et al: Vidarabine therapy of neonatal herpes simplex virus infection. Pediatrics 1980 Oct; 66:495-501

Whitley RJ, Nahmias AJ, Visintine AM, et al: The natural history of herpes simplex virus infection of mother and newborn. Pediatrics 1980 Oct; 66:489-494

Campylobacter Enteritis

Campylobacter jejuni is a recent addition to the differential diagnosis of inflammatory enteritis and is already recognized as a major cause of enteritis in humans. Several recent studies indicate that *Campylobacter* can be cultured from the stools of 4 percent to 14 percent of patients with diarrhea, a larger percentage than that for either *Salmonella* or *Shigella*.

The term campylobacter is derived from Greek words meaning "curved rod." The older literature classified *C jejuni* in the genus *Vibrio* because of morphologic similarities to *V cholera*. Differences in biochemical and growth characteristics have led to the creation of a separate genus, *Campylobacter*. The organisms that cause human enteritis used to be classified as *Campylobacter fetus* subspecies *jejuni*. Recently they have been elevated to a separate species *Campylobacter jejuni*.

Before 1977 *C jejuni* were missed on cultures of stool specimens because of their nonstandard growth requirements. Identification is usually accomplished by using a selective medium containing antibiotics to suppress other intestinal flora in an atmosphere containing 5 percent oxygen and at a temperature of 42°C. Many laboratories will not routinely plant stool cultures under these conditions. Thus a special request to culture for *C jejuni* may have to be made by the physician ordering the culture.

The route of transmission of *C jejuni* is not entirely clear. Fecal-oral transmission and contaminated food and water are considered to be major ways. The organism is widespread among animals, both as commensal gastrointestinal flora and as a cause of enteritis. A large outbreak in Vermont was traced to a contaminated water supply. Dogs with enteritis have been implicated in other studies. Person-to-person transmission, especially among children, is well documented.

Patients of all ages are affected, with peak incidence for children occurring during the first 5 years of life and for adults at 20 to 25 years. Most cases occur during the summer months.

Clinical presentation varies from mild to severe disease. Incubation is usually one to six days. A febrile prodrome with headache, malaise and variable temperature elevation is common. This is followed by abdominal pain and diarrhea that begins with watery and profuse stools. Dysenteric stools develop after a few days. Gross blood and mucus are present in the stools of most patients at some time during the course of the illness. Severe colicky abdominal pain is a hallmark of *Campylobacter* enteritis. The pain can be severe enough to mimic an acute condition of the abdomen. Laparotomies in search of a ruptured viscus are common. Dehydration and vomiting may occur in a few patients. Fecal leukocytes are present in most cases where examinations have been carried out. Diagnosis is made by culture of stool specimens.

Duration of symptoms is usually seven to ten days. Some patients, however, have a relapsing course for several months. *Campylobacter* persists in the stools of patients after recovery but for a shorter period than *Salmonella*. Children in a Montreal study excreted bacteria for an average of 26 days, while 90 percent of Swedish patients had negative cultures after five weeks. Isolation of *C jejuni* from the stool of asymptomatic persons is rare.

C jejuni in vitro are sensitive to several antibiotics, notably erythromycin and tetracycline. Controlled trials have shown that stool cultures become negative and symptoms cease in 48 hours when erythromycin is administered orally. Duration of symptoms was not significantly different in treated and untreated patients when therapy was begun four or more days after the onset of symptoms. However, fecal shedding was considerably shortened by erythromycin treatment. At present antibiotics are usually reserved for patients with severe or protracted illness but may be useful in reducing horizontal transmission.

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REFERENCES

Anders BJ, Lauer BA, Paisley JW, et al: Double-blind placebo-controlled trial of erythromycin for treatment of *Campylobacter* enteritis. Lancet 1982 Jan 16; 1:131-132

Drake AA: Diarrhea due to *Campylobacter fetus* subspecies *jejuni*. Mayo Clin Proc 1981 Jul; 56:414-423

Pai CH, Sorger S, Lackman L, et al: *Campylobacter* gastroenteritis in children. J Pediatr 1979 Apr; 94:589-591

Rettig PJ: *Campylobacter* infections in human beings. J Pediatr 1979 Jun; 94:855-864

Svedhem A, Kaijser B: *Campylobacter fetus* subspecies *jejuni*: A common cause of diarrhea in Sweden. J Infect Dis 1980 Sep; 142:353-359

Treatment and Prognosis of Reye's Syndrome

REYE'S SYNDROME is an acute noninflammatory encephalopathy associated with fatty change in the liver. It occurs in previously healthy, vigorous children and ranks behind only acute infectious encephalitis as the most common cause of death in virus-related diseases of the central nervous system (CNS). The early recognition of this syndrome by primary care physicians, coupled with organized protocols of therapy, has resulted in decreased mortality in recent years.

Reye's syndrome is heralded by protracted vomiting followed by alternating periods of lethargy and excitability in a child with a trivial, antecedent viral illness. Geographic and temporal clusters are associated with influenzae A and B. Noncluster cases occur throughout the year asso-

ciated with other illnesses such as varicella gastroenteritis. Salicylates have been implicated by some investigators in the pathogenesis of Reye's syndrome, but direct proof is lacking. The diagnosis should be strongly suspected in a nonjaundiced child with a clinical history compatible with Reye's syndrome and SGOT, SGPT and serum ammonia levels greater than twice the upper limits of normal. Supporting laboratory data include a prolonged prothrombin time, serum bilirubin level less than 3 mg per dl, hypoglycemia and normal cerebrospinal fluid. If not clear, the diagnosis may be confirmed by percutaneous liver biopsy that shows microvesicular fat accumulation. Mimicking conditions, including varicella-associated CNS and hepatic dysfunction, can thus be excluded.

Rapid deterioration through progressive stages of coma culminating in irreversible or lethal neurologic damage is usually associated with elevation of intracranial pressures (ICP). Therapy therefore hinges on relief of increased ICP, assessed by an ICP monitoring device, and is most efficiently accomplished in a regional intensive care unit with a critical care team following an anticipatory protocol. Principal modalities for the relief of elevated ICP currently include osmotherapy with mannitol and controlled hyperventilation. Some centers also use hypothermia, short-acting barbiturates and decompressive craniectomy.

These approaches have been associated with a decrease in mortality during the past 5 years from approximately 40 percent to 20 percent or less. The stage of coma at which intensive supportive care is begun appears to influence the prognosis. While progression to deeper stages of coma is common following institution of therapy, admission in stages of deep coma is associated with higher mortality. The incidence of neurologic dysfunction following recovery from Reye's syndrome is not well established. School performance may be affected in children who otherwise show no disability, and severe motor disorders may persist in those who progressed to stages of deep coma.

These considerations prompt the following recommendations: Recognition of Reye's syndrome requires a child's immediate admission to hospital, intravenous administration of 10 percent dextrose and half-normal saline solution at a maintenance rate (1,500 ml per sq meter per 24 hours) and careful monitoring of mental and cardiopulmonary status. Early consultation with and transfer to a referral center familiar with management of Reye's syndrome is appropriate because of the complexity of treatment and implications for a good outcome.

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REFERENCES

Corey L, Rubin RJ, Hattwick MA: Reye's syndrome: Clinical progression and evaluation of therapy. Pediatrics 1977 Nov; 60: 708-714

Crocker JF: Reye's Syndrome II. New York City, Grune and Stratton, 1979

Decongestants and Antihistamines in the Care of Acute or Serous Otitis Media

DECONGESTANTS AND ANTIHISTAMINES are commonly used in the treatment of otitis. Pneumatic otoscopy and tympanometry have improved a clinician's ability to diagnose serous otitis media (SOM). SOM develops in about 20 percent to 50 percent of children after an episode of acute otitis media (AOM). A child under age two is more likely to have a persistent effusion, but no studies currently indicate the long-term prognosis.

Recently several studies have examined prevention of SOM following AOM by giving drug or placebo along with antibiotic treatment for AOM. Not every study used the objective criterion of tympanometry. When compared with placebo, there was no substantial reduction in the occurrence of SOM after two weeks for pseudoephedrine hydrochloride or sulfate, brompheniramine maleate, tripolidine hydrochloride or a tripolidine-pseudoephedrine (Actifed) combination.

Randall in a similar manner tried to prevent AOM by initiating antihistamine-decongestant (brompheniramine-phenylephrine-phenylpropanolamine [Dimetapp]) treatment when symptoms of an upper respiratory tract infection were felt. When compared with placebo, there was no significant decrease in the development of AOM.

The medical treatment of SOM, once it is established, has been equally frustrating. In their studies, Olson and co-workers kept children with SOM after AOM on a drug or placebo for an additional four to six weeks. Neither pseudoephedrine nor brompheniramine improved the rate of cure. The subgroup who had a past history of SOM actually did worse on either treatment compared with placebo. Fraser and colleagues also failed to show either Dimetapp, ephedrine nose drops or auto inflation (by obstructing the nose and blowing to open the eustachian tube) as useful in British children with SOM. However, children with long-standing SOM may have underlying allergies

or eustachian tube dysfunction and may differ briefly from a child with SOM after acute otitis. We need more study of this group with chronic SOM.

In summary, based on these studies there is no supporting evidence thus far for using antihistamines, decongestants or their combinations for (1) the prevention of AOM when a cold develops, (2) the prevention of SOM when AOM is being treated or (3) the treatment of SOM once it develops.

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REFERENCES

Chilton LA, Skipper BE: Antihistamines and alpha-adrenergic agents in treatment of otitis media. South Med J 1979 Aug; 72(8): 953-955

Fraser JG, Mehta M, Frazer PM: The medical treatment of secretory otitis media—A clinical trial of 3 commonly used regimes. J Laryngol Otol 1977; 91:757-765

Klein SW, Olson AL, Perrin J, et al: Prevention and treatment of serous otitis media with an oral antihistamine—A double-blind study in pediatric practice. Clin Pediatr 1980 May; 19(5):342-347

Olson AL, Klein SW, Charney E, et al: Prevention and therapy of serous otitis media by oral decongestant: A double blind study in pediatric practice. Pediatrics 1978 May; 61(5):679-684

Randall JE, Hendley JO: Abstract presented to Ambulatory Pediatric Association, New York, NY Apr 24-25, 1978

Yersinia Enteritis in Children

YERSINIA-ASSOCIATED gastroenteritis is caused by *Yersinia enterocolitica* or *Yersinia pseudotuberculosis*. Both organisms are related to the causative agent of plague, *Yersinia pestis*. The organisms may be confused with Gram-negative nonlactose-fermenting enteric pathogens but are distinguished by their growth in specifically defined media or under cold enrichment. *Y pseudotuberculosis* produces an invasive lesion in experimental animals with granulomas in mesenteric nodes. A heat-stable toxin that is biochemically similar to other enteric pathogens has been isolated from human strains of *Y enterocolitica* and the organism can also produce lesions of the lymphatic system of the gastrointestinal tract and mesenteric lymph nodes.

In the United States *Y enterocolitica* enteritis in children seems to be an infrequent cause of diarrhea. In a survey of enteropathogens at Children's Hospital National Medical Center in Washington from 1974 to 1976, only five cases of diarrhea were described with *Y enterocolitica*. Four of these five children had primary enteric illness, while the fifth patient had associated ocular and joint involvement. In three of five cases the disease was self-limited. Two of the five patients seemed to respond to antimicrobial therapy with either orally administered ampicillin or trimethoprim-sulfamethoxazole. In other series, the acute enteritis is characterized by fever (87 percent), diarrhea (69 percent), severe abdominal pain (62 percent), vomiting (56 percent) and other constitutional symptoms such as pharyngitis, headache and leukocytosis. Blood may be present in stools. The average illness lasts from one to two days and subsides spontaneously without sequelae. Yersinia-associated enteritis is reported most frequently in cold months. Both *Y pseudotuberculosis* and *Y enterocolitica* have been identified from a wide range of animal and environmental sources, including domesticated animals such as pigs, goats and dogs and contaminated animal products such as goat's milk, chocolate milk or contaminated water sources. Person-to-person spread appears to be unusual. The incubation period is between five and seven days for both of these pathogens.

Two other presentations of *Y enterocolitica* infection occur. One is a syndrome of abdominal pain more common in older children and adolescents. This illness generally begins with abdominal pain, fever and vomiting; diarrhea may not be a prominent feature. The pain often localizes to the lower quadrants and may mimic mesenteric adenitis, terminal ileitis or a true appendicitis. Intestinal perforation or metastatic spread of infection may develop. The other, less frequent, presentation of *Yersinia* infection is characterized by the development of systemic manifestations in addition to enteritis. The clinical spectrum may range from erythema nodosum with mild or moderate arthritis to involvement of the eye with iritis and conjunctivitis. Classical Reiter's syndrome may develop and appears to be associated with persons who possess the HLA-B27 antigen.

Yersinia-associated gastroenteritis should be suspected in any case of febrile diarrheal illness and in cases of acute abdominal pain simulating appendicitis. If mesenteric adenitis, appendicitis or ileitis is found at surgery, appropriate cultures should be taken. *Yersinia* can be isolated with cold enrichment (4°C for three weeks) and grows on MacConkey medium or Salmonella-Shigella medium incubated at 22° to 29°C. Antibody titers can be measured by agglutination or hemagglutination and may be available through public health laboratories. Maximum antibody titers are usually present at two weeks. Most strains of both pathogens are sensitive in vitro to chloramphenicol, the aminoglycosides, trimethoprim-sulfamethoxazole and tetracycline; susceptibility to the cephalosporins, semisynthetic penicillins and ampicillins is

variable. Although efficacy of antibiotics in treating Yersinia-associated enteritis has not been established, most would recommend therapy in severe infections.

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REFERENCES

Maki M, Vesikari T, Rantala I, et al: Yersiniosis in children. Arch Dis Child 1980 Nov; 55:861-865

Marks MI, Pai CH, Lafleur L, et al: *Yersinia enterocolitica* gastroenteritis: A prospective study of clinical, bacteriologic, and epidemiologic features. J Pediatr 1980 Jan; 96:26-31

Toxic Shock Syndrome in Children and Adolescents

FIRST DESCRIBED by Todd and co-workers in 1978, the toxic shock syndrome is a new disease entity with well-defined epidemiologic and clinical criteria for diagnosis. In the original description, seven children presented with staphylococcal infection. Two of these children had focal staphylococcal abscesses, and local infection resulted in a fulminant disease that affected many organ systems. The disease today is recognized primarily in young, menstruating women using tampons. The incidence of this condition in other patients not associated with tampon usage is not known.

The clinical features and case definition criteria for toxic shock syndrome are as follows: (1) fever (temperature 38.9°C [102°F]), (2) rash (diffuse macular erythroderma), (3) desquamation (one to two weeks after onset of illness, particularly of palms and soles), (4) hypotension (less than fifth percentile by age for children 16 years of age or younger, or orthostatic syncope), (5) three or more of the following types of involvement: *gastrointestinal* (vomiting or diarrhea, or both, at onset of illness), *muscular* (severe myalgia or creatine phosphokinase twice normal), *mucous membrane* involvement (vaginal oropharyngeal or conjunctival hyperemia), *renal* (blood urea nitrogen or creatinine levels twice normal or urinalysis showing greater than five leukocytes per high-power field in the absence of a urinary tract infection), *hepatic* (total bilirubin, serum aspartate aminotransferase [formerly, serum glutamic oxaloacetic transaminase, SGOT] or serum alanine aminotransferase [formerly, serum glutamic pyruvic transaminase, SGPT] twice normal), *hematologic* (platelets less than 100,000 per cu mm), *central nervous system* (disorientation or alterations in consciousness without focal neurologic signs), negative results from *blood, throat* or *cerebral spinal fluid cultures; negative serologic tests* for Rocky Mountain spotted fever, leptospirosis or measles.

Most patients recover completely within 7 to 14 days. Desquamation may be patchy but occasionally involves almost the entire body. Hair loss and nonreversible nail defects have also been reported.

The incidence of toxic shock syndrome in menstruating women is estimated at 3 per 100,000 per year. Since this is a low figure compared with tampon usage, additional factors must play a role. The association with colonization or infection with phage group 1 *Staphylococcus aureus* is clear. If toxigenic *S aureus* is the causative factor, how does tampon use predispose to the disease? Investigations have shown that regular use of tampons and of so-called superabsorbent tampons produce vaginal mucosal drying and epithelial changes. The superabsorbent tampons may produce microulcerations that facilitate local extension of vaginal staphylococcal colonization to the circulatory system.

Toxic shock syndrome is a multisystem disease varying in severity and with a variety of historical, physical and laboratory manifestations. It is similar to other desquamative conditions such as Kawasaki's disease (mucocutaneous lymph node syndrome), the scalded-skin syndrome, cat scratch disease, scarlet fever, Rocky Mountain spotted fever, leptospirosis and staphylococcal food poisoning. The above conditions must be ruled out and can be excluded by appropriate laboratory tests. Retrospective analysis of other patients in the literature thought to have one of the above mentioned desquamative conditions now fulfill the criteria of toxic shock syndrome and the incidence of the disease will increase as more data are reviewed.

Investigations are now concerned with the production of a staphylococcal toxin that is probably responsible for the disease. The pyogenic and exfoliative toxins associated with *S aureus* infection have not been isolated consistently in patients with the toxic shock syndrome. Perhaps a new yet unidentified toxin is responsible for the clinical manifestations of the disease.

Therapy of toxic shock syndrome depends on the severity of the illness. Severe cases require intensive care facilities, with initial therapy directed toward correction of hypotension. Oncotic pressure should be monitored and vasopressors

are used to maintain perfusion. Antistaphylococcal antibiotics are used, although they may be more important to minimize the risk of recurrent disease. The use of corticosteroids is controversial.

Current recommendations for women who prefer to continue tampon use are as follows: use of sanitary napkins during sleep hours; if toxic shock syndrome has been previously diagnosed, tampons should not be used for at least two cycles and only after cultures are negative for *S aureus*.

Patients who have focal staphylococcal infections should be monitored closely for the possibility of development of the fulminant toxic shock syndrome.

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REFERENCES

Tofte RW, Williams DN: Toxic shock syndrome: Clinical and laboratory features in 15 patients. Ann Intern Med 1981 Feb; 94: 149-156

Shands KN, Schmid GP, Dan BB, et al: Toxic-shock syndrome in menstruating women—Association with tampon use and *Staphylococcus aureus* and clinical features in 52 cases. N Engl J Med 1980 Dec 18; 303:1436-1442

Gysler M: Toxic shock syndrome—A synopsis. Pediatr Clin North Am 1981; 28:433-435

Todd J, Fishaut M, Kapral F, et al: Toxic shock syndrome associated with a phage-group-I-Staphylococci. Lancet 1978 Nev 25; 2(8100):1116-1118

Glasgow LA: Staphylococcal infection in the toxic shock syndrome (Editorial). N Engl J Med 1980 Dec 18; 303:1473-1474

Martin GI, Schapiro SC: Another example of serious Group A Staphylococcal disease. J Pediatr 1976; 89:862

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EDITORIALS

The Dilemma of Local Control of Breast Cancer

SUCCESSFUL TREATMENT of breast cancer begins with local control. Improvements in the survival will require the addition of metastatic control therapy to effective local management. The treatment of breast cancer can involve a range of options, the choice of which is an area of controversy only partially resolvable by the study of available clinical research information.

The treatment of breast cancer can be divided into three separate aspects: (1) control of the lesion in the breast, (2) control of metastasis to the axillary lymph nodes and (3) control of metastasis to the internal mammary nodes. To just speak about local control, ignoring the heterogeneity just described, is to oversimplify what is a highly complex subject. Local control in the above three areas needs to be viewed from two perspectives. The first is the effectiveness of local treatment per se, as shown by the lack of local recurrence. The second is recognizing the importance of initial local control in relation to treatment of metastasis. Put another way, the question is what impact local control in the three areas has on ultimate metastatic relapse.

For many years halstedian principles rigidly dictated the local therapy of breast cancer. This meant that the entire breast had to be removed, including a complete en bloc axillary dissection and removal of the pectoralis major muscle. This was the classic radical mastectomy. The apogee of the halstedian approach was the extended radical mastectomy in which the en bloc nodal dissection was enlarged to include the internal mammary nodes. In recent years the most common operation carried out in the United States has been the so-called modified radical mastectomy in which an axillary dissection is done within the limitations of not splitting the pectoralis muscle. Another surgical procedure that has come into use and has been reported is total, or simple, mastectomy —in which the breast is removed along with a sampling of axillary lymph nodes. Lesser surgical procedures include segmental resection, quadrantectomy, tylectomy, lumpectomy and excisional biopsy. All of these involve removing the primary tumor and a certain amount of surrounding breast tissue, but leaving the remaining breast.

After any of the surgical procedures mentioned above, irradiation is an option to be considered and debated. After any of the mastectomy procedures the goal of adjunctive x-ray therapy is to diminish the incidence of local recurrence in the chest wall and in the regional nodes. After the more conservative (breast sparing) procedures, the additional role of x-ray therapy is to prevent the occurrence of occult tumor in the residual breast tissue.

Table 1 lists the various local treatment options that are described in the literature, and currently being studied, for the three separate aspects of local control. The potential combinations that can be derived from these options are 90. Each of these 90 options needs to be evaluated from the two distinct perspectives of the effectiveness of local control per se and its impact on metastatic control. When searching the literature for resolution of the conflicts inherent in the potential options, one is struck by the truth of the often-quoted statement made by Dr. Bernard Fisher

that "breast cancer is an area of strong opinion and weak data."

In this issue Deffebach, Goodman and Miller make a strong case for the use of excisional biopsy and irradiation as an approach to local treatment of primary breast cancer. The great bulk of evidence in support of this position comes from retrospective analysis of experiences at single institutions.

It must be recognized that trials in primary breast cancer may require ten years or more before definitive analysis. While the early recurrence rate may be helpful in analysis, only long-term survival is definitive. Analysis of these trials must also take into account the heterogeneity of primary breast cancer. Subset analysis requires adequate numbers in the various breakdowns of important prognostic variables. These prognostic variables include the size of the primary tumor, the clinical and pathologic status of the axillary lymph nodes, the patient's menopausal status and the estrogen-receptor content.

Properly designed trials are one of the most important, if not the most important, aspects in analyzing the treatment results in primary breast cancer. The trials should be prospectively randomized with an appropriate control group of a standard therapeutic approach. Most of the data on excisional biopsy and irradiation are uncontrolled and thus are open to the criticism of selection bias. If 100 consecutive patients are seen and 50 selected for a new treatment, there is

TABLE 1.—*Therapeutic Options for Local Control of Breast Cancer That Exist in Current Clinical Research*

Breast	*Axillary Nodes*	*Internal Mammary Nodes*
1. Mastectomy	1. Axillary dissection	1. Surgical dissection
2. Segmental resection or quadrantectomy or excisional biopsy plus breast irradiation with or without implantation boosting	2. Axillary dissection plus irradiation	2. Irradiation
3. Irradiation alone*	3. Irradiation	3. No initial therapy
	4. "Sampling" or incomplete axillary dissection	
	5. No initial therapy (treat relapse as appropriate)	

All of the above plus or minus chemotherapy that may affect local control

*Exclusively in French literature.

TABLE 2.—*Ongoing Clinical Trials of Importance to Issues of Control of Breast Cancer*

I. National Surgical Adjuvant Breast Project

Clinical node-negative or node-positive women with primary lesions ≤4 cm

R → Segmental resection + axillary sampling
R → Segmental resection + axillary sampling + irradiation
R → Total mastectomy + axillary sampling

Most important *potential* therapeutic implication:
Leaving residual breast tissue untreated after removal of primary tumor may provide adequate local control.

II. National Cancer Institute

Clinical node-negative or node-positive women

R → Radical mastectomy
R → Excisional biopsy + axillary dissection + irradiation with breast implantation

Most important *potential* therapeutic implication:
A breast-salvage procedure will be equivalent to radical mastectomy.

R = randomization.

the chance that these 50 patients were selected to be optimally responsive to the therapy. This can be compounded if the referral pattern for a given new procedure being done in a major center shifts toward patients deemed optimal for the therapy.

In analyzing single-arm retrospective series with irradiation as primary treatment for breast cancer, it is impossible to gauge fully the degree of selection bias. The fact that the results of the primary irradiation therapy series are comparable with those reported for mastectomy is reassuring but not definitive. For example, if the irradiated patients have smaller primary tumors or other favorable prognostic variables, the comparability of results with large mastectomy series with a different mix of prognostic variables may be diminished. The matching that is done in the literature of single-arm series of irradiation with mastectomy series is a crude one at best. It involves only one or two factors such as stage I versus II or negative nodes versus positive ones. Other issues of selection are ignored, as are the problems of quality control in therapy delivery, follow-up time, follow-up techniques and data-reporting procedures.

The only appropriate way to remove the problem of selection bias is to carry out prospectively randomized studies so that those treated with mastectomy are comparable with those treated with irradiation in all aspects except the two treatments under question. Unfortunately, data from such trials do not exist, with one exception.

The exception is the Milan Trial recently reported.[1] In this trial women with $T_1N_0M_0$ lesions (primary tumor 2 cm or less) were selected. They were assigned randomly to receive either radical mastectomy or quadrantectomy, axillary node dissection and external irradiation of the breast. With data from five years the two treatment options have given comparable local and metastatic recurrence rates. Survival is also identical. The cosmetic results of removing a quarter of the breast are clearly superior to those obtained after radical mastectomy, with the caveat that the follow-up time is still short, for primary breast cancer. This trial does indicate that irradiation is a viable option for women with small primary lesions.

Two studies are currently being done in the United States that are testing the question of primary irradiation. These are the trials of the National Surgical Adjuvant Breast Project (NSABP) and the National Cancer Institute (Table 2). It is hoped that these trials will provide better answers than currently exist.

Unfortunately, the debate about the treatment of primary breast cancer has taken on the emotional overtones of women's rights and freedom of choice. This public debate ignores totally the heterogeneity of breast cancer and the available data. What is worse, the emotionalism impedes the clinical research that will have to be done if the questions are to be adequately answered. There is no clearly optimal therapy for primary breast cancer. It is still a halfway technology and we are still learning.

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REFERENCE

1. Veronesi U, Saccozzi R, Del Vecchio M, et al: Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med 1981 Jul 2; 305:6-11

Coalitions for Health Care

UNLIKELY AND UNREAL as it might seem, there may be a bright spot beginning to emerge on the troubled and baffling scene of rising health care costs. In an unprecedented move six major national organizations have found common ground for concern over the escalating cost of health care at a time when the expenditures are taking an increasing portion of the nation's gross national product. The six organizations are the American Medical Association, the American Hospital Association, the Blue Cross and Blue Shield Associations, the Health Insurance Associations of America, the Business Roundtable and the AFL-CIO. The emphasis is to be on encouraging voluntary coalitions at the local, state and regional levels. The following is extracted from a statement agreed to by these organizations:

We endorse, in this period, the potentials of voluntary coalitions on a local, state or regional basis. We encourage our members or local affiliates to participate together in such coalitions, recognizing that at the outset local conditions and relationships may appropriately result in different configurations, patterns of membership and programs. But, in due course, for effective results, all concerned groups need to be included. An individual organization is unlikely to have the same impact if acting alone.

They further state

the most appropriate focus of local coalitions generally to be the costs of delivery of medical care, and the numerous factors which locally influence such costs, with related attention to the quality of care, to the availability of proper medical care and access to such care by various groups within the population.

It is suggested that the coalitions begin with an analysis of local health systems and then develop a "limited agenda of a very few priority projects," presumably these being ones which all agree can and should be accomplished.

This approach seems like quite a bit of fresh air. It recognizes the interdependence within the health care system and that no one segment of it is likely ever to be able to control all of it. It recognizes that no single solution or plan is ever likely to meet the needs of all the nation's regions, states or local communities. It involves, or should involve at each level, all those who, if anything is to be accomplished, must (1) agree that there is a problem, (2) define what it is, (3) decide what should be done about it, how it can be done and who will do what, (4) carry out the agreed-upon decision and (5) monitor the progress being made toward solving the problem. And, not the least important, it recognizes that physicians with their special training and expertise in health care should, and indeed must, be part of the decision-making process in this, as in every aspect of health care.

The first step will be for these more or less disparate organizations to meet and get to know one another at each level and to develop a common understanding of what problem or problems are to be addressed and gather a common data base of the pertinent existing information. From this common ground there can then come some workable solutions which will be reasonably acceptable to all concerned, since they all will have shared in the process which led to a consensus about exactly what the problem is and what is to be done about it. And since these coalitions will involve many or most of those who are in a position to carry out the consensus, the results could be impressive.

It is now abundantly clear that there are no real shortcuts to controlling the escalating cost of health care—that is, if quality, availability and access are to be maintained and improved. Any real progress is likely to be found in the aggregate of many small and some not so small efforts by many persons in many places. It is therefore appropriate that these problems begin to be addressed at the more local levels (where they are more manageable in size and scope) by those who can understand them and who are in a position to do something about them.

—MSMW

Does Coronary Artery Bypass Grafting Improve Survival?

WHEN THE HISTORY of medicine of the 20th century is written, the chapter on coronary artery bypass grafting (CABG) will surely be important and interesting. This chapter will show American medicine at both its best and its worst. At its best it reflects inventiveness, ingenuity, daring and technical skill, all of a very high order; at its worst, its rapid dissemination reflects the medical profession's acceptance of an expensive, sometimes hazardous form of therapy before an objective appraisal has been made of efficacy for each of its several indications. Somewhat belatedly, but certainly better late than never, CABG is now undergoing sober appraisal. The thoughtful review by Carr, Engler and Ross that appears in this issue is a valuable contribution in this regard. We have likened the explosive proliferation of CABG early in the 1970's to the escape of the genie from Aladdin's bottle,[1,2] and these authors have contributed to the current effort to put some reins on this genie (it may be too late to stuff it back into the bottle).

There is little disagreement that CABG is remarkably effective in relieving anginal pain and is therefore indicated in many patients who do not respond to medical therapy. The difficulty is not with the severely symptomatic patients, but rather with the asymptomatic or mildly symptomatic ones who have critical obstructions in the coronary arteries. Such patients constitute at least half, perhaps two thirds, of patients currently undergoing CABG in this country. One can approach the question of the efficacy of CABG in this large group first by considering the natural history of coronary artery disease. Survival with this condition depends on the amount of residual normally contracting myocardium.[3] Both experimental[4] and clinicopathologic[5,6] studies have shown that infarction of less than 20 percent of the left ventricular myocardium can be sustained with no or little detectable change of overall left ventricular function at rest; losses of approxi-

mately 20 percent to 40 percent generally result in varying degrees of left ventricular failure, necrosis of more than 40 percent often produces cardiogenic shock and destruction of more than 50 percent to 55 percent of the left ventricle is usually fatal.

With these considerations in mind, an important principle emerges from the clear-cut beneficial effects on survival of CABG in patients with left main coronary artery disease and the lack of any perceptible improvement in prognosis when patients with single-vessel disease are operated on. In the former condition, the viability of a large portion of the left ventricle is at risk of a single occlusive event. Occlusion of the narrowed lumen, a not unlikely event in a progressive disease such as atherosclerosis, would impair the viability of such a large portion of the left ventricular myocardium that pump failure and death might be anticipated.[7] But the necrosis resulting from the occlusion of the residual lumen of a single narrowed coronary artery should leave sufficient left ventricle to sustain life in most cases. If the other two vessels are normal, the patient's prognosis should be excellent. Therefore, even if the surgical mortality were reduced to zero in patients with single-vessel disease and the postsurgical survival were identical to that of an age-matched normal population, a very large number of such patients would be needed to be able to prove any potential benefits of CABG. In contrast, the superiority of surgical therapy should be readily evident in patients with left main coronary artery disease, especially those with some impairment of left ventricular function, if the procedure largely eliminated the hazard of the single occlusive event and even if surgical mortality were as high as 10 percent.

Additional points concerning the natural history of patients with coronary artery disease require consideration. These include the following:

- The relative stability of the process that, in turn, may be related to the rate of progression of the underlying obstructive lesion. It is likely that the reported relatively favorable prognosis of asymptomatic patients, on the one hand,[8] and the poor outlook of those with progressively worsening symptoms[9] on the other, reflects the importance of this factor. As a consequence of the more aggressive use of noninvasive screening tests, particularly stress electrocardiography, perfusion scintigraphy and radionuclide ventriculography, an increasing number of patients with anatomic evidence of coronary disease but few if any symptoms are now subjected to coronary arteriography and thus identified. Also, arteriography is done with increasing frequency on asymptomatic survivors of uncomplicated myocardial infarction and on patients with cerebrovascular disease and peripheral arteriosclerosis who have no cardiac symptoms. The above-mentioned evidence[8] suggests that the prognosis in asymptomatic patients is more favorable than in symptomatic patients, reducing the potential effectiveness of CABG in improving survival.

- There is increasing evidence that chronic beta-adrenergic blockade favorably influences the prognosis in survivors of myocardial infarction.[10] It is not unreasonable to propose that these drugs have similar favorable effects in other subsets of patients with ischemic heart disease as well. Beta blockers are now used extensively in the treatment of hypertension and angina and it is possible that they are exerting a beneficial effect on many patients, making the effects of operation on long-term survival more difficult to discern.

- A new class of antianginal drugs, the calcium-channel blockers, has just been released.[11,12] These agents, whose actions are quite distinct from those of the beta blockers, appear to exert additive effects in the relief of symptoms of myocardial ischemia. Because their adverse effects are relatively mild, it is likely that they too will be used widely and might further improve the prognosis of patients with ischemic heart disease by increasing oxygen delivery to the myocardium through coronary vasodilatation, lowering arterial pressure and exerting antiarrhythmic actions. Such effects are likely to narrow further the differences in survival between medically and surgically treated patients with coronary atherosclerosis.

- Surgical technique continues to improve, perhaps less dramatically than in the early 1970's, but nonetheless perceptibly. Even patients with significant impairment of left ventricular function and those requiring as many as six or seven grafts can now be expected to survive operation, with a low mortality rate (under 3 percent), improved myocardial perfusion, patent grafts and a low incidence of perioperative infarction. Furthermore, though there is still a good deal of variability in the outcome of surgical treatment among various institutions and surgical teams, competitive pressures are weeding out those teams whose results are distinctly below the norm.

Given the large gaps in our knowledge concerning the natural history of coronary disease, the drift in the patients under consideration for operation toward a higher proportion of asymptomatic people and the progressive efficacy of both medical and surgical treatment, what principles can the physician follow in selecting patients with CABG today? To list just a few:

- Assuming that a patient's age and general condition do not preclude operation, CABG should be carried out in patients who continue to experience angina despite intensive medical therapy and whose coronary arteriograms and ventricular function indicate that they are anatomically suitable.
- A bypass grafting procedure is also indicated in patients with more than 50 percent narrowing of the left main coronary artery, regardless of the presence of angina.
- CABG should *not* be carried out on asymptomatic or mildly symptomatic patients with obstructive disease involving a single coronary artery, unless that vessel perfuses an unusually large segment of the left ventricle.
- The treatment of asymptomatic or mildly symptomatic patients with two- or three-vessel disease must be individualized. The principal characteristics that make the physician lean toward recommending CABG include (*a*) a larger volume of jeopardized viable myocardium perfused by vessels that are extremely narrowed (obstruction greater than 90 percent); (*b*) left ventricular dysfunction, with an ejection fraction below 50 percent, but above 25 percent; (*c*) troubling side effects of therapeutic drugs, patient intolerance of medical therapy or poor compliance; (*d*) history of a myocardial infarction; (*e*) age below approximately 45 years; (*f*) excellent record of the surgical team with the type of patient under consideration, and (*g*) a patient's inclination towards operation.

Although information that is likely to become available in the next few years will probably clarify the indications for CABG in this large group of patients in whom we are still "flying by the seats of our pants," perhaps we can get some solace now from considering that in all likelihood the relative advantages of medical and surgical treatments in most of these patients are almost equally balanced, and that there is relatively little to choose between one or the other. As the wide gaps of knowledge in this important field are narrowed, the indications for CABG will become progressively more refined. Nevertheless, there will always be a subset of patients with coronary artery disease in whom the results of medical or surgical treatment that can be anticipated will be similar. Then, as now, the thoughtful management of these patients will require the combination of a thorough knowledge of each patient, including a detailed consideration of pathoanatomy; the extent, if any, of left ventricular dysfunction; a patient's life style, hopes, fears and expectations, and the record of the surgical team.

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REFERENCES

1. Braunwald E: Direct coronary revascularization—A plea not to let the genie escape from the bottle. Hosp Pract 1971; 6(5):9-10

2. Muller JE, Stone PH, Markis JE, et al: Let's not let the genie escape from the bottle—again. N Engl J Med 1981; 304: 1294-1296

3. Geltman EM, Ehsari AA, Campbell MW, et al: The influence of location and extent of myocardial infarction on long-term ventricular dysrhythmia and mortality. Circulation 1979; 60:805-814

4. Pfeffer MA, Pfeffer JM, Fishbein MC, et al: Myocardial infarct size and ventricular function in rats. Circ Res 1974 Apr; 44(4):503-512

5. Page DL, Caulfield JB, Kastor JA, et al: Myocardial changes associated with cardiogenic shock. N Engl J Med 1971; 285:133-137

6. Harnarayan C, Bennett MS, Pentecost BL, et al: Quantitative study of infarcted myocardium in cardiogenic shock. Br Heart J 1970; 32:728-736

7. Hutter AM Jr: Is there a left main equivalent? Circulation 1980 Aug; 62:207-211

8. Epstein SE, Kent KM, Goldstein RE, et al: Strategy for evaluation and surgical treatment of the asymptomatic or mildly symptomatic patient with coronary artery disease. Am J Cardiol 1979 May; 43(5):1015-1025

9. Harris PJ, Harrell FE Jr, Lee KL, et al: Survival in medically treated coronary artery disease. Circulation 1979; 60: 1259-1269

10. The Norwegian Multicenter Study Group: Timolo-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981; 304:801-807

11. Antman EM, Stone PH, Muller JE, et al: Calcium channel blocking agents in the treatment of cardiovascular disorders—Part I. Basic and clinical electrophysiologic effects. Ann Intern Med 1980; 93:875-885

12. Stone PH, Antman EM, Muller JE, et al: Calcium channel blocking agents in the treatment of cardiovascular disorders—Part II: Hemodynamic effects and clinical implications. Ann Intern Med 1980; 93:886-904

Interstitial Lung Disease

Aggressive Clinical Management Versus Diagnostic and Therapeutic Nihilism

THE INTERSTITIAL LUNG DISEASES are chronic, usually progressive, disorders of the lung parenchyma characterized by alveolitis and derangements of the lung parenchyma with fibrosis.[1,2] As

more and more alveoli are affected, dyspnea develops, first with exercise and later at rest. About this time the affected person seeks medical attention.

What should be done? The answer lies in understanding the pathogenesis of these diseases and the armamentarium now available to the clinician in dealing with such patients.

The history is critical. There are more than 100 known causes of interstitial lung disease.[1] In some cases (for example, a patient is taking one of the many drugs that cause interstitial disease) the disease can be stabilized, and sometimes reversed, by simply removing the offending agent.

For most patients with interstitial disease encountered in an average medical practice, however, no cause can be identified. It is for this group that rational diagnostic and therapeutic decisions are most difficult. The key to making these decisions is the understanding that it is the inflammatory and immune effector cells making up the alveolitis that are responsible for most of the derangements to alveolar structures that characterize these disorders.[1-6]

There are three important aspects to the alveolitis of interstitial lung disease: (1) an expansion in the number of effector cells present in the lower respiratory tract, (2) a shift in the types of effector cells present and (3) an activation of many of these effector cells. In normal nonsmoking people, the effector cell population of the alveolar structures consists of two types: alveolar macrophages (90 percent of the effector cells) and lymphocytes (the remaining 10 percent).[5] With some overlap, the alveolitis of the interstitial lung diseases can be grouped roughly into two categories—the lymphocytic disorders and the neutrophilic disorders.

The alveolitis of the lymphocytic disorders (for example, sarcoidosis, hypersensitivity pneumonitis, berylliosis) is generally composed of expanded numbers of lymphocytes and alveolar macrophages, a shift toward greatly increased proportions of T lymphocytes and an activation of both lung T cells and macrophages.[4-8] The large numbers of activated lung T cells and macrophages cause these disorders to progress: the T cells modulate granuloma formation while the alveolar macrophages modulate T-cell replication, thus maintaining the expansion of the lung T-cell population.

In contrast with the lymphocytic disorders, the alveolitis of the neutrophilic disorders (for example, idiopathic pulmonary fibrosis) also comprises expanded numbers of activated alveolar macrophages, together with the presence of neutrophils (a cell rarely found in the alveolar structures).[3,7,9] The chronic presence of neutrophils is devastating to the lower respiratory tract. Neutrophils release a broad array of mediators including proteases that derange most classes of connective tissue (the extracellular skeleton of the alveolar structures) and oxidants that injure parenchymal cells. Unlike alveolar macrophages of the lymphocytic disorders, the activated alveolar macrophages of the neutrophilic disorders do not greatly expand lung T-cell numbers, but rather modulate the extensive fibrosis that is especially characteristic of the neutrophilic disorders. By recruiting fibroblasts and expanding their numbers in the alveolar structures, the alveolar macrophages play a role in the attempted reconstruction of the devastation mediated by the neutrophils. In many cases, however, the derangement to the alveolar structures is so great that the reconstruction processes are out of synchrony in time and location, resulting in extensive scarring of the lower respiratory tract. Furthermore, by releasing a chemotactic factor that recruits neutrophils,[9] the alveolar macrophage of the neutrophilic disorders maintains the neutrophil burden of the alveolar structures and hence the continued devastation of the normal architecture.

In the context of understanding the importance of alveolitis in the pathogenesis of these disorders, it is apparent that the most important task for the clinician caring for a patient with interstitial lung disease is to characterize and stage the alveolitis. How can this be accomplished? Lung biopsy is one approach, but the size of the transbronchial biopsy specimen limits its usefulness and the risk and morbidity associated with open-lung biopsy precludes its use in following these cases. Unfortunately, the classic tools of the pulmonary physician, x-ray studies of the chest and pulmonary function testing, are neither sensitive to nor specific for alveolitis.[2,10] Rather, they detect the result of alveolitis—that is, the derangements to the alveolar structures caused by the effector processes of the inflammatory and immune cells that comprise the alveolitis.

If clinicians cannot accurately characterize and stage the alveolitis of these patients, is any evaluation useful? Is the nihilistic approach to interstitial disease therefore warranted? Ten years ago perhaps. But with the advent of gallium 67 scan

ning and bronchoalveolar lavage, it is now a simple process to characterize alveolitis and stage its activity.

Gallium 67 scanning takes advantage of the fact that gallium 67 localizes to sites of inflammation. In normal persons, little gallium localizes in the lung parenchyma. In individuals with interstitial lung disease with active alveolitis, however, there is usually a diffuse uptake of gallium 67 in the alveolar structures, most readily apparent on a scan done 48 to 72 hours after administration of the isotope.[11,12] Recent evidence suggests that this occurs principally because the activated alveolar macrophage localizes the tracer.[13]

Bronchoalveolar lavage is a simple extension of fiberoptic bronchoscopy.[5,7] After local anesthesia and evaluation of the airways, the bronchoscope is wedged in a distal bronchus and approximately 100 ml of sterile saline (usually in 5 or 20 ml aliquots) is infused into the bronchoscope and immediately aspirated. This process washes out some of the epithelial fluid from approximately 10^6 alveoli and, with it, the inflammatory and immune effector cells that comprise the alveolitis. Using conventional cytologic procedures, the total cells recovered are measured and a cell differential determined.

Together gallium 67 scanning and bronchoalveolar lavage give an excellent overview of the character of the alveolitis of the interstitial lung disorders.[2] Neither are diagnostic, but by identifying the type of alveolitis, the diagnostic possibilities are narrowed and, most importantly, accurate staging of the activity of the alveolitis is possible. In this context, on the average, patients with interstitial lung disease with active alveolitis have a progressive downhill course, while those with inactive alveolitis either stabilize or improve.[2,4,14,15] Because alveolitis mediates the damage to the alveolar structures and because alveolitis is amenable to therapy (for example, corticosteroids), by characterizing the type of alveolitis the physician obtains critical information regarding prognosis and the need for therapy.

Furthermore, these procedures can be used repeatedly to gauge response to therapy. This is a great advantage in treating these patients, because the therapies used often have serious side effects and render a patient susceptible to opportunistic infections.

It is apparent that the days of diagnostic and therapeutic nihilism are gone and aggressive clinical management is both warranted and effective in dealing with the interstitial lung disorders. But, as in all medical specialties, the clinician must balance aggressiveness with its attendant risks and costs. In an 81-year-old patient with rheumatoid arthritis in whom interstitial lung disease develops (such as the woman discussed in the Clinical Management Conference in this issue), the overwhelming diagnosis is that the interstitial disease is a manifestation of collagen vascular disease. While the pathogenesis of the interstitial disease in such persons is not known, it is clearly associated with a mild neutrophilic alveolitis.[7,16] Should such a patient be subject to transbronchial biopsy? No, too little tissue will be obtained to stage the alveolitis. Open biopsy? Probably not, the risk and morbidity is not worth it and the information can be derived by other means. Should we do gallium 67 scanning or bronchoalveolar lavage or both? Why not? The risks and morbidity are trivial, both give an assessment of the alveolitis and thus yield information critical to the management of the patient. Are they cost effective? The answer is not yet in, but unlike the vast majority of laboratory studies usually carried out in such patients, these approaches yield specific information that the clinician can directly apply to patient management. And that is what efficient, rational clinical management is all about.

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REFERENCES

1. Keogh BA, Crystal RG: Chronic interstitial lung disease, *In* Simmons DH (Ed): Current Pulmonology, Vol 3. New York, Wiley, 1981, pp 237-340

2. Crystal RG, Gadek JE, Ferrans VJ, et al: Interstitial lung disease: Current concepts of pathogenesis, staging, and therapy. Am J Med 1981; 70:542-568

3. Crystal RG, Fulmer JD, Roberts WC, et al: Idiopathic pulmonary fibrosis—Clinical, histologic, radiographic, physiologic, scintigraphic, cytologic, and biochemical aspects. Ann Intern Med 1976 Dec; 85:769-788

4. Crystal RG, Roberts WC, Hunninghake GW, et al: Pulmonary sarcoidosis: A disease characterized and perpetuated by activated lung T-lymphocytes. Ann Intern Med 1981; 94:73-94

5. Hunninghake GW, Gadek JE, Kawanami O, et al: Inflammatory and immune processes in the human lung in health and disease: Evaluation by bronchoalveolar lavage. Am J Pathol 1979; 97:149-206

6. Keogh BA, Crystal RG: Alveolitis: The key to the interstitial lung disorders. Thorax 1982 (In Press)

7. Reynolds HY, Fulmer JD, Kazmierowski JA, et al: Analysis of cellular and protein content of broncho-alveolar lavage fluid from patients with idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. J Clin Invest 1977 Jan; 59:165-175

8. Hunninghake GW, Crystal RG: Pulmonary sarcoidosis: A disorder mediated by excess helper T-lymphocyte activity at sites of disease activity. N Engl J Med 1981 Aug 20; 305:429-434

9. Hunninghake GW, Gadek JE, Lawley TJ, et al: Mechanisms of neutrophil accumulation in the lungs of patients with idiopathic pulmonary fibrosis. J Clin Invest 1981; 68:259-269

10. Keogh BA, Crystal RG: Pulmonary function testing in interstitial pulmonary disease: What does it tell us? Chest 1980; 78:856-865

11. Line BR, Fulmer JD, Reynolds HY, et al: Gallium-67 citrate scanning in the staging of idiopathic pulmonary fibrosis: Correlation with physiologic and morphologic features, and bronchoalveolar lavage. Am Rev Respir Dis 1978 Aug; 118:355-365

12. Line BR, Hunninghake GW, Keogh BA, et al: Gallium-67 scanning to stage the alveolitis of sarcoidosis: Correlation with clinical studies, pulmonary function studies, and bronchoalveolar lavage. Am Rev Respir Dis 1981; 123:440-446

13. Hunninghake GW, Line BR, Szapiel SV, et al: Activation of inflammatory cells increases the localization of gallium-67 at sites of disease (abst). Clin Res 1981; 49:171A

14. Keogh BA, Hunninghake GW, Line BR, et al: Alveolitis parameters as predictors of the natural history of pulmonary sarcoidosis (abst). Clin Res 1981; 49:447A

15. Keogh BA, Line BR, Rust M, et al: Clinical staging of patients with idiopathic pulmonary fibrosis (abst). Am Rev Respir Dis 1981; 123 (part 2):89

16. Weinberger SE, Kelman JA, Elson NA, et al: Bronchoalveolar lavage in interstitial lung disease. Ann Intern Med 1978; 89:459-466

How Cost Effective Are the Hassles of Practice?

A THOUGHTFUL SURVEY by Denson and Manning appearing elsewhere in this issue draws attention to the extent that problems other than those directly related to the care of patients occupy the minds and the time of practicing physicians. The extent is considerable and disturbing. By far the largest number of the 2,745 physicians surveyed reported government regulation of medical practice as the most significant current problem in their practices while only a very small minority placed diagnosis, therapy or doctor-patient relationships as their most important concerns. What might be called the hassles of today's practice environment made up most of the other top problems cited by these physicians, and they together with government regulation of medical practice make up the overwhelming majority of what are seen as the most significant problems of practice.

One can only conclude that there is an enormous amount of wasteful and no doubt costly friction in the machinery of daily practice as it is done today. Most of this friction is generated by forces impinging upon what might be called nuclear patient care—the interaction that takes place between a doctor and a patient who is seeking advice or care. Most of these forces are seen to arise from the external environment of medical practice and represent social, economic or political interventions usually for the purpose of controlling costs or, less often, to assure quality, which now have become more or less accreted to the machinery of patient care. One can only wonder how much or how often this superimposed friction really results in better or less expensive care. There are few data on either the cost or the benefit, but Denson and Manning have pointed to a problem.

—MSMW

CASE REPORTS

Refer to: Taylor RF, Buckner CD: Fat overload from 10 percent soybean oil emulsion in a marrow transplant recipient. West J Med 1982 Apr; 136:345-349

Fat Overload From 10 Percent Soybean Oil Emulsion in a Marrow Transplant Recipient

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MARROW TRANSPLANTATION is a complex procedure that frequently requires intensive supportive care, including nutritional support. The Seattle transplant group routinely places a large-bore right atrial catheter for prophylactic administration of total parenteral nutrition including the use of a 10 percent soybean emulsion (Intralipid, manufactured by Cutter Medical Division of Cutter Laboratories, Berkeley, California 94710).[1] We describe our first case of the so-called fat-overload syndrome from Intralipid administration.

Report of a Case

A 25-year-old man was admitted to the Fred Hutchinson Cancer Research Center in July 1979 for allogeneic marrow transplantation for severe aplastic anemia. The presumed cause of the aplastic anemia was viral hepatitis, though toxic hepatitis could not be excluded. The hepatitis B surface antigen was negative and a test for surface antibody was positive. At the time of admission, leukocytes numbered 300 per cu mm, the platelet count was 68,000 per cu mm following transfusion and the hematocrit was 22.4 percent. The serum bilirubin was 2.4 mg per dl, the alkaline phosphatase was 131 IU per liter (N, 13 to 39), the serum aspartate aminotransferase (formerly serum glutamic oxaloacetic transaminase, SGOT) was 58 IU per liter (N, 0 to 41), the lactate dehydrogenase (LDH) was 175 IU per liter (N, 60 to 220) and the serum creatinine was 1.2 mg per dl (N, 1 to 2). Blood cultures were positive for *Escherichia coli*. A right atrial catheter was placed on the day of admission and total parenteral nutrition was begun the following day with 25 percent dextrose, a 4.25 percent crystalline amino acid solution (FreAmine II) and 500 ml of Intralipid per day.[1] He was treated with broad spectrum antibiotics. Marrow transplantation was carried out a week later (day 0) as previously described.[2]

The first month posttransplantation was relatively uneventful, with clearing of the Gram-negative septicemia and return of the results of liver function tests to the normal range, except for an LDH between 160 and 500 IU per liter. On day 18 a skin biopsy was found to be positive for graft-versus-host disease. This syndrome remained clinically mild without specific therapy until day 29 when the administration of methylprednisolone, 160 mg a day, was begun because of abdominal pain and diarrhea presumed to be due to graft-versus-host disease. At this time the serum bilirubin was 1.0 mg per dl, the alkaline phosphatase was 217, SGOT 27 and LDH 236 IU per liter and the serum creatinine was 0.8 mg per dl. Despite steroid therapy the diffuse rash progressed, the diarrhea increased to 2 liters per day and the serum bilirubin rose to 5.0 mg per dl, with an SGOT of 126 and alkaline phosphatase of 459 IU per liter. These changes were attributed to graft-versus-host disease, and on day 40 the patient was started on the administration of horse antithymocyte globulin (Upjohn) at a dosage of 15 mg per kg of body weight per day through day 53 and every other day until day 61.

On day 42 the quantity of Intralipid was increased to 1 liter a day. At this time the patient was critically ill with increasing liver dysfunction, ascites and large volumes of bloody diarrhea (2 to 3 liters a day). He had adequate marrow function.

Concomitant with antithymocyte globulin ad-

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ministration, the rash and liver disease lessened but not the diarrhea. By day 53 the serum bilirubin was 0.8 mg per dl, the alkaline phosphatase was 188, SGOT 21 and the LDH 196 IU per liter. Amphotericin B administration was begun on day 69 because of persistent fever and cultures of the blood were positive on day 70 for *Candida tropicalis*. On day 64 the LDH rose to 618 IU per liter and continued to rise, reaching a peak of 4,390 on day 74. At the same time the SGOT rose from 219 to 310 IU per liter and the bilirubin from 0.9 to 3.4 mg per dl. By day 75 the serum creatinine was 2.9 mg per dl and the blood urea nitrogen (BUN) was 76 mg per dl (N, 8 to 25), with a good urine volume.

On day 71 his serum was noted to be lipemic and burgundy colored, and administration of Intralipid was discontinued. On day 73 the serum was still lipemic, hemolysis was still present and the serum triglyceride level was 483 mg per dl (N, 40 to 150).

LDH fractionation showed pronounced increases in all fractions. Serum creatine phosphokinase, amylase, calcium and phosphorus were all normal. Coagulation studies showed a prolonged partial thromboplastin time, thrombin time and reptilase time, with a normal fibrinogen and prothrombin time. Peripheral blood smears showed many nucleated red blood cells and vacuolated polymorphonuclear leukocytes. An oil red 0 stain of the peripheral blood smear was positive for neutral fat both within the vacuoles of granulocytes and in the plasma. The patient's red blood cells showed burr cell formation (see Figure 1). An osmotic fragility curve was abnormal, with increased hemolysis at sodium chloride concentrations greater than 0.6 percent, and 20 percent hemolyzed cells were present at 0.8 percent normal saline solution. On day 72 the patient had abdominal pain and shortness of breath. Oxygen pressure (Po_2) with the patient breathing room air was 47.5 mm of mercury and carbon dioxide pressure (Pco_2) was 33.1 mm of mercury. The patient was placed on supplemental oxygen. His chest film was unchanged.

At this point it was felt that he had iatrogenic fat overload leading to respiratory insufficiency, hemolytic anemia and acute renal failure.

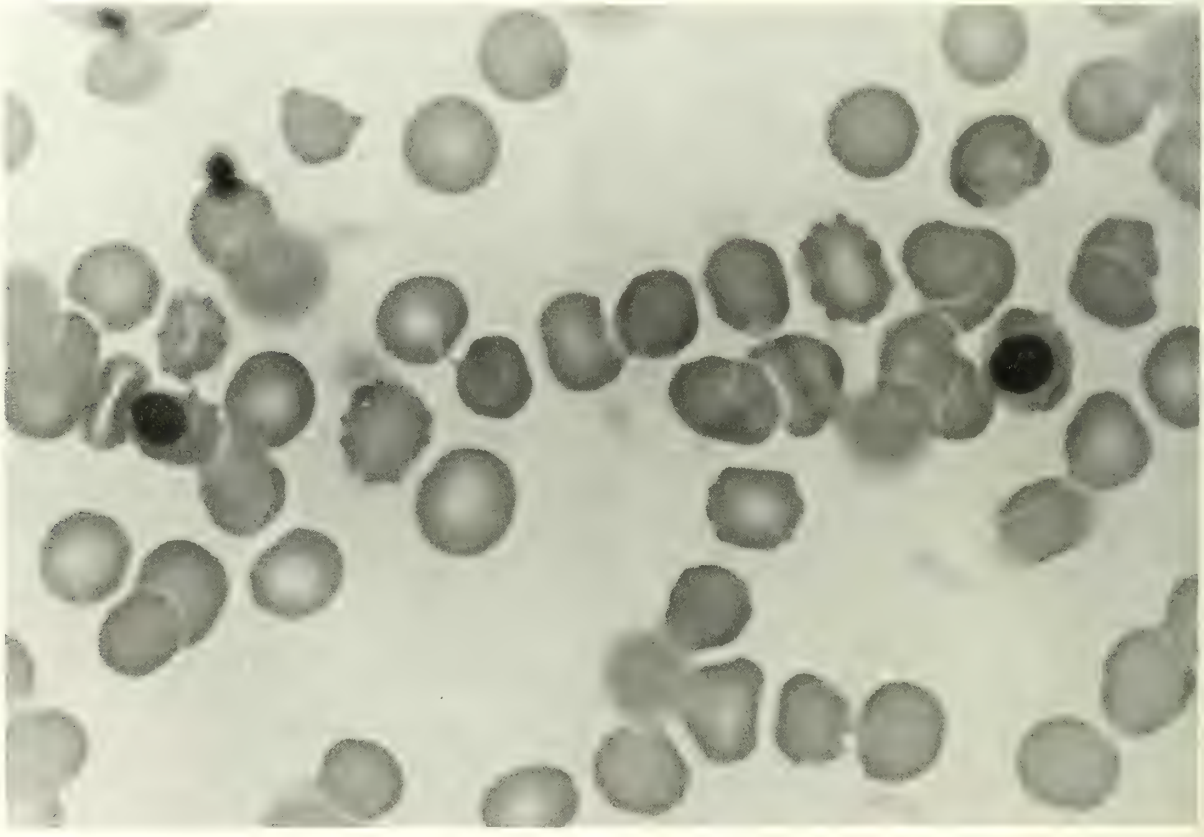

Figure 1.—Peripheral blood smear from the patient, showing several burr cells, nucleated red blood cells and schistocytes. (Reduced from magnification ×100.)

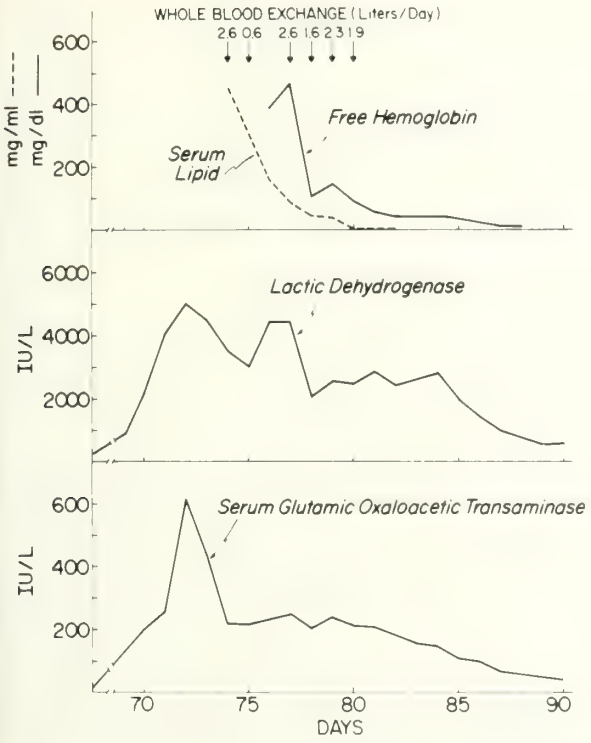

Figure 2.—The effect of whole blood exchange on serum lipid, free hemoglobin, lactic dehydrogenase and SGOT levels in a 25-year-old patient with fat-overload syndrome.

On day 74 whole blood exchanges were started to decrease the lipid and free hemoglobin and to remove damaged red cells (Figure 2). Ongoing hemolysis was detectable in the plasma until day 87.

By day 87 the plasma free hemoglobin had dropped to normal and the LDH was 1,119 IU per liter. There was pronounced improvement in pulmonary function. His renal function had not improved, however, and dialysis was begun on day 86. The patient died on day 99 of disseminated aspergillosis and graft-versus-host disease.

Discussion

Total parenteral nutrition has become an accepted means of treating the nutritional problems of patients unable to meet their caloric demands by oral intake.[3] Marrow transplant recipients represent a group of patients in whom hyperalimentation is particularly helpful and often crucial in their care. Persistent anorexia develops in many of these patients following chemoradiotherapy. Mucositis develops in others, with or without herpes stomatitis, preventing them from ingesting adequate calories. Still others, those with severe graft-versus-host disease of the gut, are unable to absorb enough calories to maintain their body mass. Many of these patients have notably increased metabolic demands either from infection, bleeding or other complications, thus making nutrition even more important.

We routinely administer total parenteral nutrition to all transplant recipients. This has been facilitated through the use of a large-bore right atrial catheter.[1] Using this technique, we have been able to substantially improve the nutrition of patients undergoing marrow transplantation.

Patients placed on total parenteral nutrition receive a crystalline amino acid solution with varying concentrations of dextrose depending on their caloric needs. In addition, we have used infusions of a 10 percent soybean oil emulsion as a means of providing additional calories and of preventing free fatty acid deficiency.[4,5] This substance has been well tolerated by most patients in most clinical settings, including ours. Surveys of patients receiving lipid emulsion therapy have supported its safety and efficacy as a means of providing isoosmotic calories.[6]

Attempts to administer free fatty acids to patients date back to the introduction of various vegetable oil preparations. The early preparations were associated with severe toxicity, including hyperpyrexia, embolic phenomena and renal failure. Soybean oil emulsions were introduced in 1935[7] as a means of supplementing amino acid solutions in protein-sparing therapy. These substances provided advantages over standard hyperalimentation solutions in that they were isoosmotic and could thus be given through a peripheral vein. They have high caloric content per unit volume and, when given in addition to amino acid solutions, provide a balanced nutritional program. In addition, administration of lipid emulsions was a means of preventing essential fatty acid deficiency, a syndrome described in patients receiving only amino acid solutions.[8,9] In contrast to their predecessors, the newer lipid preparations were associated with only minimal toxicity.

Sporadic reports have indicated that lipid emulsions affect a variety of organ systems. Several studies have shown that lipids given in this manner can depress T cell function.[10] One author reported increased platelet adhesiveness following lipid emulsion administration.[11] Animal studies have suggested that 10 percent intravenous fat emulsions have been associated with pulmonary hypertension and arterial hypoxemia.[12] A recent

report has shown decreased phagocytosis by macrophages when pretreated with a lipid preparation.[13]

A report of a lipid-overload syndrome was published by Belin and colleagues in 1976.[14] They described a patient in whom hypoxemia, oliguria, liver function abnormalities and coagulation defects developed following the infusion of a lipid emulsion. The syndrome resolved after cessation of lipid therapy.

Marks and co-workers[15] have recently described three cases of anemia and reticulocytosis in patients receiving lipid emulsions. These patients were also noted to have transient liver function abnormalities but did not experience renal or pulmonary dysfunction. In each case, the syndrome resolved without additional therapy following discontinuation of the lipid preparation.

Hessov and associates[16] have reported postmortem findings in three patients who had received lipid emulsions before they died. These patients displayed a pattern of fat deposition including large deposits in the heart, kidneys and small blood vessels. Each had severe underlying disease contributing to death.

Thus, it seems that there are certain pathologic states that are associated with altered lipid tolerance. Studies of lipid clearance in liver disease and following trauma suggest that lipid clearance is actually increased, presumably due to increased demands. Patients with Gram-negative septicemia and renal failure, however, seem less able to clear lipid from their blood. In the case described by Belin and colleagues,[14] the patient tolerated the lipid infusion well for a long period of time, only to become acutely overloaded for reasons that are not clear.

These reports indicate that one of the difficulties with lipid administration in parenteral nutrition is the lack of accurate monitoring techniques. While periodic nephelometric measurements seem to provide relatively good correlation with lipid concentration in vitro, they often fail to give the same correlation in vivo.[17] Visual assessment of changes in turbidity suffer from observer variation even with experienced personnel. Monitoring of fatty acid levels is expensive and time consuming.

Of interest in the present case is the appearance of burr cells and hemolysis. A particularly abnormal osmotic fragility curve was also noted in this patient, suggesting a membrane defect. These findings cleared after the removal of plasma lipid.

One of the distressing aspects of this case is the suddenness with which the syndrome developed, despite relatively little change in the patient's clinical status. If one examines LDH levels as an indicator of hemolysis, this process actually began several days before the serum was noted to be lipemic, and at a time when the SGOT value was normal. This emphasizes the inadequacy of visual inspection of the serum as a means of evaluating lipid tolerance.

The effectiveness of treatment of the syndrome remains discouraging. In the present case, whole blood exchange was undertaken in an attempt to remove lipid. Despite aggressive exchanges, however, the patient still required more than a week to clear his plasma entirely. This time course correlates reasonably well with that described by Belin and co-workers in the patient whose blood was not exchanged.[14] While the lipid load in our patient may have been greater than that described by Belin, his slow clearance may have simply resulted from the relative inaccessibility of the lipid-to-plasma clearing techniques.

After clearing of the patient's serum of lipid, the results of liver function studies, coagulation factors and peripheral blood smear showed improvement. But the renal failure persisted and may have been an irreversible consequence of the hemolytic episode.

While lipid emulsions seem to provide an appealing addition to the hyperalimentation program, like any intravenous therapy they are not without adverse effects. The lack of an accurate and readily available means of monitoring tolerance in critically ill patients remains a problem.

Summary

A fat-overload syndrome developed from infusion of 10 percent soybean emulsion in a 25-year-old patient who had a marrow transplant for aplastic anemia. This condition resulted in hyperlipidemia, respiratory distress, hemolytic anemia and acute renal failure. These events complicated an already complex posttransplant course. All the signs and symptoms except the acute renal failure reversed after whole blood exchange. The patient died of disseminated aspergillosis complicated by severe graft-versus-host disease.

REFERENCES

1. Hickman RO, Buckner CD, Clift RA, et al: A modified right atrial catheter for access to the venous system in marrow transplant recipients. Surg Gynecol Obstet 1979 Jun; 148:871-875

2. Storb R, Thomas ED, Weiden PL, et al: Aplastic anemia treated by allogeneic bone marrow transplantation: A report on 49 new cases from Seattle. Blood 1976 Dec; 48:817-841

3. Ota DM, Imbembo AL, Zuidema GD: Total parenteral nutrition. Surgery 1978 May; 83:503-520

4 Goodgame JT, Lowry SF, Brennan MF: Essential fatty acid deficiency in total parenteral nutrition: Time course of development and suggestions for therapy. Surgery 1978 Aug; 84:271-277

5. Wene JD, Conner WE, DenBesten L: The development of essential fatty acid deficiency in healthy men fed fat-free diets intravenously and orally. J Clin Invest 1975; 56:127-134

6. Hallberg D, Holm I, Obel AL: Fat emulsions for complete intravenous nutrition. Postgrad Med J 1967; 43:307-316

7. Holt E, Tidwell HD, McNair S: The intravenous administration of fat: A practical therapeutic procedure. J Pediatr 1935; 6:151-160

8. O'Neill JA Jr, Caldwell MD, Meng HC: Essential fatty acid deficiency in surgical patients. Ann Surg 1977; 185:535-542

9. Jeejeebhoy KN, Zohrab WJ, Langer B, et al: Total parenteral nutrition at home for 23 months, without complication, and with good rehabilitation—A study of technical and metabolic features. Gastroenterology 1973 Nov; 65:811-820

10. Mertin J, Hunt R: Influence of polyunsaturated fatty acids on survival of skin allografts and tumor incidence in mice. Proc Natl Acad Sci USA 1976 Mar; 73:928-931

11. Cronberg S, Nilsson IM: Coagulation studies after administration of fat emulsion, intralipid. Thromb Diath Haemorrh 1967; 18:664-669

12. McKeen CR, Brigham KL, Bowers RE, et al: Pulmonary vascular effects of fat emulsion infusion in unanesthetized sheep —Prevention by indomethacin. J Clin Invest 1978 May; 61:1291-1297

13. Strunk RC, Payne CM, Nagle RB, et al: Alteration of the structure and function of guinea pig peritoneal macrophages by a soybean oil emulsion. Am J Pathol 1979 Sep; 96:753-770

14. Belin RP, Bivins BA, Jona JZ, et al: Fat overload with a 10% soybean oil emulsion. Arch Surg 1976 Dec; 111:1391-1393

15. Marks LM, Patel N, Kurtides ES: Hematologic abnormalities associated with intravenous lipid therapy. Am J Gastroenterol 1980; 73:490-495

16. Hessov I, Melsen F, Haug A: Postmortem findings in three patients treated with intravenous fat emulsions. Arch Surg 1979 Jan; 114:66-68

17. Schreiner RL, Glick MR, Nordschow CD, et al: An evaluation of methods to monitor infants receiving intravenous lipids. J Pediatr 1979 Feb; 94:197-200

Refer to: Welk SW: *Achromobacter* pneumonia. West J Med 1982 Apr; 136:349-350

Achromobacter Pneumonia

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PNEUMONIA IS ONE of the illnesses most frequently resulting in hospital admission. Yet, the specific cause of this common clinical condition is often difficult to determine, especially in small community hospitals where the laboratory experience and materials may be limited. Sensitivity profiles may, however, provide clues to the diagnosis and successful treatment of pneumonia.

Achromobacter xylosoxidans, first identified by Yabuuchi and Oyama[1] in 1971, is a Gram-negative bacillus and may be confused with *Pseudomonas* organisms. In fact, their sensitivity profiles may be quite similar, with the notable exception of their differing sensitivities to sulfa drugs. Recognition of *Achromobacter*'s characteristic sensitivity profile may help distinguish these two very similar organisms.

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Submitted May 8, 1981.

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TABLE 1.—*Sensitivity of* Achromobacter xylosoxidans

Antimicrobial Drugs	*Sensitivity*
Amikacin	R
Ampicillin	R
Carbenicillin	S
Cefamandole	I
Cephalothin	R
Chloramphenicol	R
Clindamycin	R
Erythromycin	R
Gantrisin	S
Gentamicin	I
Kanamycin	R
Oxacillin	R
Penicillin	R
Trimethoprim/sulfamethoxazole (Septra)	S
Tetracycline	R
Tobramycin	I
Vancomycin	R

R = Resistant I = Intermediate S = Sensitive

Report of a Case

A 71-year-old woman who had never smoked was seen with a three-day history of fever, cough and anorexia. There was production of between 2 and 3 oz of thick, grayish brown sputum per day. There was a documented weight loss of 18 kg (40 lbs) over the past two years. There were at least ten previous episodes of pneumonia, several occurring in childhood. An extensive workup for weight loss and possible malignancy had been conducted previously, with completely negative findings on all testing, including cultures and cytology of sputum for tuberculosis, a body scan and α_1-antitrypsin immunology test. Other medical problems included a benign cyst of the maxillary sinus plus hiatus hernia with reflux and esophagitis controlled with cimetidine.

On admission the patient was noted to be pale, febrile and dyspneic at rest. Moist rales were heard in the left lung field. X-ray studies of the chest showed two infiltrations on the right side. Leukocytes numbered 9,100 per cu mm and determination of arterial blood gases revealed moderate hypoxemia. The electrocardiogram was interpreted as showing right axis deviation, P pulmonale and low voltage, suggesting chronic pulmonary disease. Pulmonary function tests showed severely re-

stricted and obstructed lung function, with the forced expiratory volume 48 percent and vital capacity 26 percent of predicted.

Because of the suspicion of an anaerobic pneumonia, a transtracheal aspiration was done. Thick, white, sweet-smelling, almost caseous material was obtained. Culture of the aspirate grew out 4+ small Gram-negative rods. The sensitivity profile was remarkably resistant to all antimicrobial drugs except carbenicillin and sulfa drugs (see Table 1). Minimal inhibitory concentration (MIC) levels were obtained for sulfa drugs and showed pronounced sensitivity (MIC 0.5 μg/ml).

The patient was treated with trimethoprim-sulfamethoxazole (Septra) for three weeks. The lung infiltration cleared and the patient regained 11.34 kg (25 lbs). The Centers for Disease Control identified the organism two months later as *A xylosoxidans*.

Comment

A xylosoxidans is an organism only recently recognized and reported. The biochemical and morphologic features are distinguishable from *Pseudomonas* sp and were characterized by the Centers for Disease Control in 1979.[2] It may be waterborne and transmitted as recognized by Shigeta and co-workers[3] who found that it had contaminated hospital ward containers of chlorhexidine and caused cerebral ventriculitis. *A xylosoxidans* has also been found in cases of chronic otitis externa as reported by Yabuuchi and Oyama[1] and Pien and Higa.[4]

A xylosoxidans probably occurs more frequently than recognized. The clue to the diagnosis may be in the sensitivity profile, where it resembles *Pseudomonas* sp, with the notable exception of *A xylosoxidans*' sensitivity to sulfa drugs. A review of the bacteriologic sensitivity profiles at our local hospital over a two-year period showed two other organisms reported as *Pseudomonas* with comparable sensitivity profiles. Awareness of this fact may provide physicians with an early diagnosis and patients with appropriate treatment.

REFERENCES

1. Yabuuchi E, Oyama A: *Achromobacter xylosoxidans* n. sp. from human ear discharge. Jpn J Microbiol 1971 Sep; 15:477-481

2. Chester B, Cooper LH: Achromobacter species (CDC group VD): Morphological and biochemical characterization. J Clin Microbiol 1979 Mar; 9:425-436

3. Shigeta S, Yasunaga Y, Honzumi K, et al: Cerebral ventriculitis associated with *Achromobacter xylosoxidans*. J Clin Pathol 1978 Feb; 31:156-161

4. Pien FD, Higa HY: *Achromobacter xylosoxidans* isolates in Hawaii. J Clin Microbiol 1978 Feb; 7:239-241

Refer to: Frolich H, Gourley RT, Hansen KS: Wegener's granulomatosis with polycythemia. West J Med 1982 Apr; 136:350-353

Wegener's Granulomatosis With Polycythemia

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ERYTHROCYTOSIS can be a sign of a primary myeloproliferative disorder or can be associated with a multitude of other diseases.[1-3] Frequently it is not possible to determine whether erythrocytosis merely coincides with polycythemia rubra vera or whether it is due to the underlying disease.[4] We report a case of polycythemia in association with Wegener's granulomatosis. To date, we are unaware of any association between vasculitis and polycythemia.

Report of a Case

A 71-year-old woman entered the hospital in 1979 for a diagnostic lung biopsy. Her illness dated back to 1973 when she noted urinary frequency and back pain. Results of her physical examination were normal and no splenomegaly was found. Laboratory values were reported as follows: A serum creatinine was 5.6 mg per dl (N = 1 to 1.5) and the erythrocyte sedimentation rate was 103 mm per hour (N = 1 to 20). She had a proteinuria of 0.8 grams per 24 hours (N less than 1.5) and a creatinine clearance of 10 ml per minute (N = 104 to 125). The hemoglobin was 8.4 grams per dl, hematocrit was 27 percent, mean corpuscular volume (MCV) was 94 femtoliter and leukocytes numbered 5,700 per cu mm, with 62 neutrophils, 1 band form, 35 lymphocytes, 1 monocyte and 1 eosinophil; platelets numbered 395,000 per cu mm (normal 200,000 to 350,000). The peripheral blood smear showed anisocytosis and poikilocytosis with occasional burr cells and microcytes. Stools were negative for occult blood and the

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serum iron and iron binding capacity values were normal. Her anemia was presumed due to her renal insufficiency. The specimen of a renal biopsy showed focal glomerulonephritis with crescent formation.

She was treated with azathioprine and prednisone for approximately four months. The serum creatinine level fell to 2.6 mg per dl and clinically she improved. In early 1978 hemoptysis developed and pulmonary nodules were noted. Bronchoscopy and transbronchial biopsy were done but findings were nondiagnostic; the nodules resolved spontaneously. In April 1979 a nasal biopsy was done because of epistaxis and chronic rhinorrhea. Necrotic tissue was present but no tumor or granulomas were seen. By August her creatinine level had risen to 4.0 mg per dl and her urinary sediment contained red cells and casts. Roentgenogram of the chest showed multiple nodules.

She was admitted to the hospital for evaluation of her condition, whereupon physical examination showed facial plethora, right upper nasal turbinate and hard palate ulcerations. Generalized lymphadenopathy and splenomegaly were noted but the liver was not clinically enlarged. Laboratory studies elicited the following values: hemoglobin 18.1 grams per dl, hematocrit 54.8 percent, leukocyte count 23,600 per cu mm, with 79 neutrophils, 6 band forms, 10 lymphocytes and 5 eosinophils; platelets numbered 459,000. The peripheral smear showed normochromic normocytic red blood cells (RBCs) and a leukocytosis with occasional basophils and giant platelets. The sedimentation rate was 2 mm per hour. Serum electrolytes were normal, but the serum creatinine level was 4.0 mg per dl and blood urea nitrogen (BUN) 75 mg per dl. The creatinine clearance was 14.7 ml per minute and the urinalysis showed 20 to 25 RBCs per high power field, 80 to 100 white blood cells per high power field and occasional granulocyte casts. The 24-hour urine protein was 333 mg (N less than 150). The serum lactate dehydrogenase (LDH) was elevated at 265 IU per ml (N = 100 to 225) and the alkaline phosphatase was 135 IU per liter (N = 30 to 85 IU per liter).

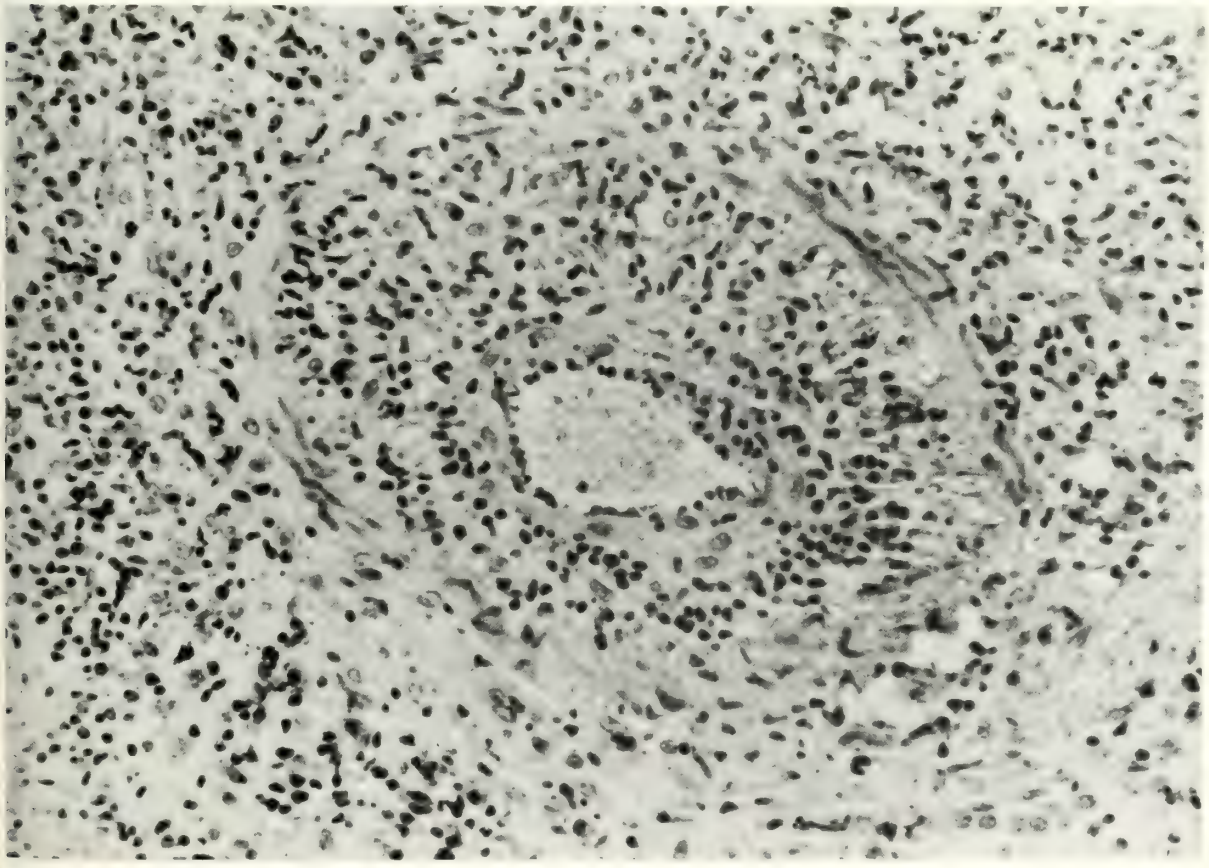

Figure 1.—Medium-sized artery with pronounced vasculitis. (Hematoxylin and eosin stain; reduced from magnification ×400.)

The red cell mass was elevated at 40 ml per kg. The arterial oxygen saturation was 92 percent (N = 96 to 100), the serum vitamin B_{12} was elevated at 2,016 pg per ml (N = 150 to 450) and the leukocyte alkaline phosphatase score was 253 (N = 15 to 225).

Antinuclear antibody and cryoglobulins were not detected and complement components C3 and C4 were found to be within normal range. An intravenous pyelogram was normal. A liver-spleen scan showed mild hepatosplenomegaly (liver span was 22 cm, N up to 21; and spleen span was 14 cm, N up to 13). A bone marrow aspiration and biopsy showed panmyelosis and a normal chromosome profile (46, XX but *no* Philadelphia chromosome).

The specimen from an open lung biopsy showed nodules with central necrosis surrounded by epithelioid histiocytes and a mixed inflammatory infiltrate. Vessel involvement consisted of fibrinoid necrosis with luminal obliteration from an inflammatory reaction (Figures 1 and 2). These findings were consistent with Wegener's granulomatosis. Review of the slides from the previous renal biopsy showed focal glomerulonephritis with one granuloma.

She was treated with cyclophosphamide with resolution of the lung nodules after two weeks. Four weeks later she suddenly died. An autopsy showed bronchopneumonia with little remaining vasculitis. There was no evidence of renal artery stenosis, renal tumor, cyst, juxtaglomerular hyperplasia, adrenal tumors or other neoplasia. The spleen was enlarged, weighing 470 grams, and showed hyperemia, generalized hyperplasia and mild fibrosis but no evidence of vasculitis. These findings were consistent with polycythemia rubra vera. The Wegener's granulomatosis in the lungs was nearly resolved.

Comment

This case is unique from two standpoints. First, the patient had a pulmonary-renal syndrome consistent with Wegener's granulomatosis in which the renal disease antedated the pulmonary pathology by six years. Second, the patient developed eryth-

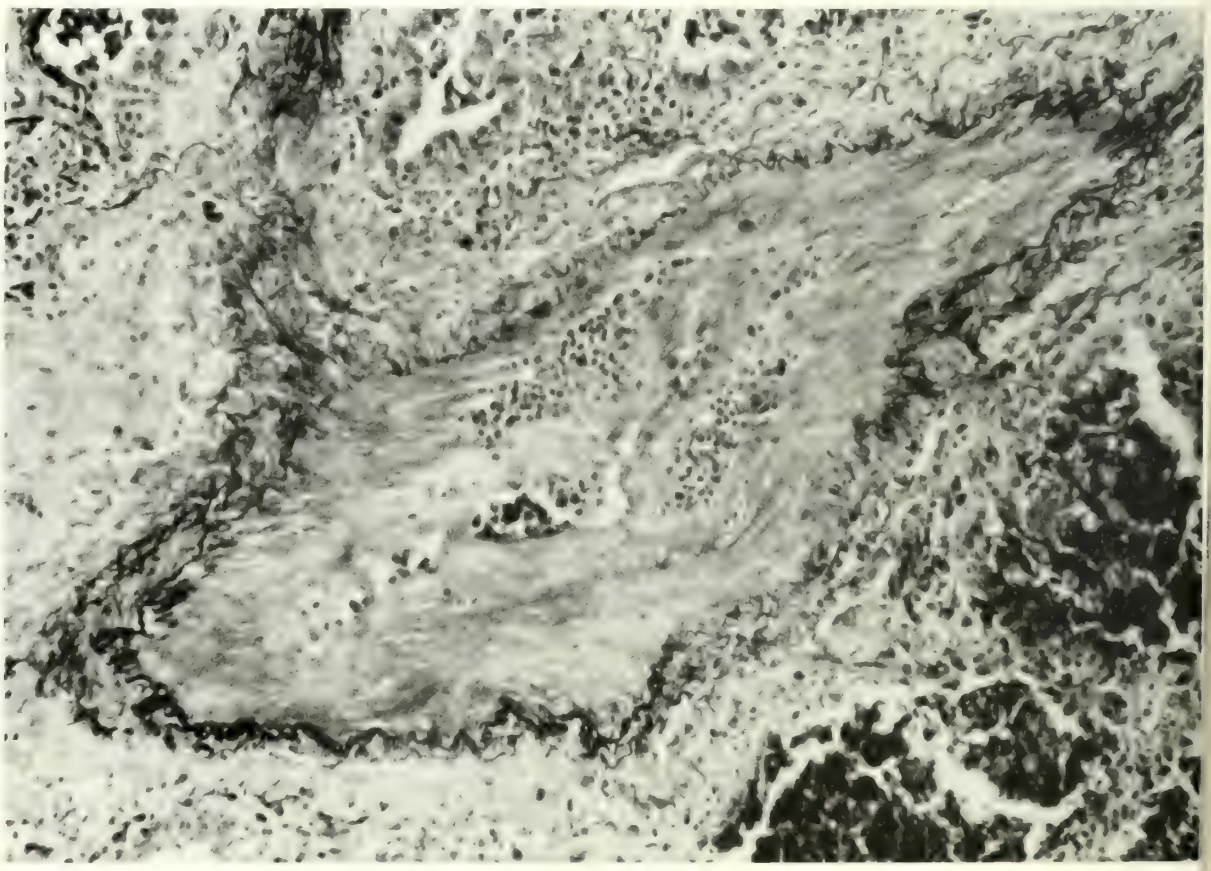

Figure 2.—Large artery with fragmentation of elastica, proliferative fibrosis, fibrinoid necrosis and marked lumina stenosis. (Van Gieson elastic stain; reduced from magnification ×100.)

rocytosis, which was consistent with polycythemia rubra vera. She fulfilled all the major and minor diagnostic criteria established by the Polycythemia Study Group for that disease.[5] It would have been interesting to have assayed the patient's urine, serum or lung tissue for erythropoietin. These unfortunately were not available to absolutely exclude a secondary form of erythrocytosis. The presence of splenomegaly, however, without associated vasculitis, and autopsy findings consistent with polycythemia rubra virtually excluded that possibility.

Erythrocytosis has been associated with various forms of parenchymal renal disease such as chronic glomerulonephritis, focal sclerosing glomerulonephritis, nephrosclerosis and Bartter's syndrome.[3] The mechanism by which erythrocytosis occurs is not always established. In fact, excess erythropoietin production, which should be the diagnostic clue to secondary erythropoiesis, could not be shown in several cases that have been reported.[6] Some have postulated that segmental renal ischemia triggers excessive erythropoietin production, thereby giving rise to polycythemia.[3] Certainly, a disease such as Wegener's granulomatosis, or any form of vasculitis that produces obliterative vascular lesions, could give rise to erythrocytosis by that mechanism. We know of no other cases in which Wegener's granulomatosis or other vasculitis syndrome has been associated with either polycythemia vera or secondary erythrocytosis.

REFERENCES

1. Thorling EB: Paraneoplastic erythrocytosis and inappropriate erythropoietin production. Scand J Haematol 1972; (Suppl 17): 89-96

2. Siggillino JJ, Crawley CJ, Claus RH, et al: Myxoma of the right atrium with polycythemia. Arch Intern Med 1963; 111:178-183

3. Sonneborn R, Perez GO, Epstein M, et al: Erythrocytosis associated with the nephrotic syndrome. Arch Intern Med 1977; 137:1068-1072

4. Wintrobe MM, Lee GR, Boggs DR, et al: Polycythemia, chap 30, *In* Wintrobe MM (Ed): Clinical Hematology. Philadelphia, Lea & Febiger, 1974, p 987

5. Berlin NI: Diagnosis and classification of the polycythemias. Semin Hematol 1975; 12:339-351

6. Basu TK, Stein RM: Erythrocytosis associated with chronic renal disease. Arch Intern Med 1974; 133:442-447

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Of *Giardia* Cysts and Sportsmen

TO THE EDITOR: *Giardia* cysts in drinking water are a widely-recognized hazard to sportsmen, and as Jarroll and co-workers[1,2] have shown, the common methods of chemical disinfection cannot be relied upon to kill the cysts in cold water. Boiling is the suggested alternative. While this is effective, hikers are reluctant to use any method which would greatly increase the burden of fuel to be carried. Indeed, many people will continue to use chemicals for this reason, in spite of the hazard.

A simple compromise is to slightly raise the temperature of the water to be treated; at 20°C, all the chemical methods tested by Jarroll and his co-workers were found to be completely effective. By bringing one fifth of the total volume of water to a boil, and mixing the hot and cold portions, a minimum temperature of 20°C will be reached with even the coldest stream water (allowance must be made for high altitudes). Chemical treatment is then carried out. Fuel expenditure is dramatically reduced, and no thermometer or large cooking vessel is necessary.

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REFERENCES

1. Jarroll EL Jr, Bingham AK, Meyer EA: *Giardia* cyst destruction: Effectiveness of six small-quantity water disinfection methods. Am Trop Med Hyg 1980 Jan; 29:8-11
2. Jarroll EL Jr, Bingham AK, Meyer EA: Inability of an iodination method to destroy completely *Giardia* cysts in cold water (Information). West J Med 1980 Jun; 132:567-569

The Devil of Nutrition Cultism

TO THE EDITOR: The publication of humorous and whimsical letters often brightens the days and late evenings of physicians who often carry numerous burdens.

It was with the presumption of a framework of whimsy that I approached the letter by John M. Douglass, MD, and others[1] in the February 1982 issue.

However, about a third of the way through, I realized I was not reading humor but either a foreign language or a set of thought processes so foreign to logic and science that it was unrecognizable as modern American medicine or modern American English.

I therefore wish to take to task the editorial staff for publishing letters written in foreign languages or in extraterrestrial logic forms without adequate translation or editoral comment.

I thank you for giving greater attention to this matter in the future.

WALLACE I. SAMPSON, MD
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EDITOR'S NOTE: Thank *you* for your editorial comment!
—MSMW

REFERENCE

1. Douglass JM, Douglass RN, Fleiss PM: The first devil of nutrition cultism (Correspondence). West J Med 1982 Feb; 136: 167-168

Beeper Bite: A Jogging Complication in Physicians

TO THE EDITOR: Immediately following a seven-mile run, a 34-year-old physician marathoner noted the presence of a 2- by 2-cm excoriated erythematous patch of skin overlying the right iliac crest. He had run with a pager (Motorola, Pageboy II) clipped to his jogging shorts, immediately overlying the site of the skin lesion. His shirtless garb put the metal clip (chromium plated aluminum) of the pager in direct contact with skin. The following day the physician ran with the pager clipped on the left side, yielding a similar eruption overlying the left iliac crest. The differential diagnosis consisted of contact dermatitis versus abrasions. The inert nature of the metallic clip and general appearance of the rash led to a diagnosis of beeper clip abrasions. Jogging continued *sans* beeper and the eruption cleared promptly.

Other therapeutic modalities may be helpful if a physician refuses to jog without beeper. Protective padding might be sewn into the shorts or strapped over the beeper with a rubber band. A shirt tucked into the shorts might help. An alternative would be to encourage the physician to

hand carry the beeper while jogging. To our knowledge, this complication of jogging has not previously been reported, but we suspect it is not an uncommon occurrence in obsessive/compulsive physician-joggers who cannot part with their beepers.

Beeper bite raises problems of morals and medical ethics. Why carry a beeper at all unless telephones are handy? Is it appropriate to ask another physician to take calls for an hour or so of jogging time, every day? Since one of the reasons for jogging is to "get away from it all" for a brief time each day, is not the act of carrying a beeper inconsistent with this goal? These issues should be carefully considered by a physician involved in a regular jogging program.

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Family Medicine for Primary Care

TO THE EDITOR: I would like to agree with Dr. Geyman's editorial comments regarding Dr. Kurtz's January article on primary care.[1,2] Dr. Kurtz has a misunderstanding of the need for family medicine as a specialty. Primary care internal medicine or pediatrics is not an acceptable alternative to family medicine.

I have lived most of my life in the rural areas of Idaho and Wyoming, and am familiar with the rural areas of Nevada and Southwestern Montana. I have received only praise from those people who live in the rural areas for choosing family medicine as my specialty.

Why? The answer is always the same: "Because we want a family doctor!" They do not want to be shifted from an internist to a pediatrician to an obstetrician or from a child health associate to a physician's assistant or a nurse practitioner to a nurse midwife. They want centralized, continuous care for themselves and their children from a family doctor, especially one who does obstetrics.

The need for family physicians is as great as the need for other specialists. Family physicians are in demand. They are cost effective, and the new family physicians are well trained.

Primary care training already exists in the excellent specialty of family medicine. There is no need for such a subspecialty in internal medicine or pediatrics. What is needed is continued growth and cooperation among the disciplines of family medicine, internal medicine, pediatrics, surgery, and obstetrics and gynecology so that quality training is available.

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REFERENCES

1. Kurtz KJ: Training the internist for primary care: A view from Nevada (Medical Education). West J Med 1982 Jan; 136: 76-82

2. Geyman JP: Training for primary care: A family practice perspective (Medical Education: Editorial Comment). West J Med 1982 Jan; 136:83-84

TO THE EDITOR: Dr. Kenneth Kurtz subtitles his recent article on primary care training[1] as "A View From Nevada." I wonder if he intended to represent Tonopah, Elko or even the communities of metropolitan Reno. From reading his article, it is apparent that his views emanate from a department of internal medicine at a university medical center.

Dr. Kurtz conceptualizes a model where nurse practitioners would possibly manage problems that require limited medical knowledge "in each sector of the family practice sphere," with single discipline specialists such as a primary care internist with five years of postgraduate training providing the rest. Do most people want or need a team that combines two extremes?

Dr. Kurtz indicates that "family practice physicians are caught in the intense squeeze of modern biomedicine." As a recent family practice residency graduate now in practice, I have not felt squeezed nor have I noticed this among my colleagues. The joy of entering practice after a family practice residency is the realization of being very well trained to manage the great majority of people's health problems. I wonder if Dr. Kurtz has stepped beyond the clinics of academia to experience this.

Dr. Kurtz also states that because of the breadth of family practice training, the result is "often a very broad, but necessarily superficial, knowledge of many aspects of medicine." I will readily admit a superficial knowledge of cryoglobulins, renal tubular acidosis, and Wegener's granulomatosis. However, along with an in-depth knowledge of the persons and families who are my patients, I know ambulatory diabetes, hypertension, obesity, degenerative arthritis, congestive heart failure, and so forth, as well as a good primary care internist.

It is unfortunate that so many internists and others in the academic setting do not accept

family practice training as legitimate in producing a competent physician. Because of this, medical students are given distorted myths and family practice residents are unnecessarily hassled. People everywhere seem to like having a good family doctor, and most of the towns in this country are too small to support any other type of physician. Apparently, physicians with three or more years of training in a single discipline cannot accept competence in a field with three years of training covering many disciplines. How many months or years of postgraduate training does it take to become competent in an area of medicine? Ironically, Dr. Kurtz feels that more than three years are necessary for competence with adult medical problems, while his residents in primary care internal medicine are likely to learn their gynecology and orthopedics in a few months.

Some academic internists have been very supportive of family practice and have greatly helped the discipline become established in medical education. An editorial by Perkoff eloquently describes this attitude.[2] As stated by Geyman[3] there will be several approaches to primary care in this country. Americans like variety and choices, and family physicians, pediatricians and internists all have their place on the front lines of medical practice. We should respect and help each other in meeting the public's needs, for if we do not I imagine that chiropractors and others will.

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REFERENCES

1 Kurtz KJ: Training the internist for primary care: A view from Nevada. West J Med 1982 Jan; 136:76-82

2. Perkoff GT: Family practice: Potential for a key role in medical care. Arch Intern Med 1981 Jul; 141:979-982

3. Geyman JP: Training for primary care: A family practice perspective. West J Med 1982 Jan; 136:83-84

Incidence of *Campylobacter* Enterocolitis

To the Editor: I enjoyed Dr. Ginsberg's short review of gastrointestinal disease and infectious diarrhea[1] in the January issue. However, the discussion on *Campylobacter fetus* subspecies *jejuni* does not emphasize the frequency of enterocolitis due to this organism. Recent data indicate that in numerous geographic areas *Campylobacter* is as common as *Salmonella* and *Shigella* combined.[2,3] Our experience in Marin County, northern California, suggests that *Campylobacter* enteritis is far more frequent than this. Two community hospitals are finding many more times *Campylobacter* versus *Shigella* and *Salmonella*. In 1981, there were 290 stool cultures processed from a 34-physician multispecialty group. Thirty-seven were positive for *Campylobacter jejuni,* one for *Shigella* and three for *Salmonella*. The cases involving *Salmonella* and *Shigella* occurred in the summer months and there was a clear epidemiological history. The cases involving *Campylobacter* were more evenly spread throughout the year, with increased frequency from September through to December. Most stool specimens positive for *Campylobacter* contained blood or polymorphonucleocytes, or both.

Frequent occurrence of disease due to *Campylobacter* in the winter months is an important issue for community clinicians. This bacterium should be considered as the most likely cause of acute diarrhea when the stool contains blood and pus. Whether erythromycin therapy should be started before culture results are obtained (often taking two to three days) has not been studied. The natural course of *Campylobacter* enteritis does not appear to be influenced by therapy started as late as four to six days after onset of symptoms.[3] Certainly our anecdotal experience suggests prompt resolution of the often debilitating symptoms when treatment has been started before the confirmation of *Campylobacter* enterocolitis by culture.

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REFERENCES

1. Ginsberg NN: Gastrointestinal disease (Epitomes of Progress—Preventive Medicine and Public Health). West J Med 1982 Jan; 136:147

2. Drake AA, Gilchrist MJR: Diarrhea due to *Campylobacter fetus* subspecies *jejuni*. Mayo Clin Proc 1981 Jul; 54:414-423

3. Laser NS, Reller LB: *Campylobacter* enteritis. N Engl J Med 1981 Dec 10; 305(24):1444-1452

Refer to: Wintrobe MM: Medical education in Utah (Medical Schools of the West). West J Med 1982 Apr; 136:357-366

Medical Education in Utah

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MEDICAL EDUCATION in the United States and Canada in the 17th and 18th centuries was based on an apprenticeship system. In due course this took the form of "walking the wards" in hospitals, some of which boasted teachers who had crossed the Atlantic and had followed the footsteps of the master physicians of Europe. Then, as early as 1750, as a supplement to apprenticeship, informal classes and demonstrations were offered in Philadelphia. Soon afterwards a medical school was established there as an organic part of an institution of learning, the College of Philadelphia, and in intimate relationship with the Pennsylvania Hospital, a large public institution. In New York and Boston, and in association with colleges at Yale, Dartmouth and elsewhere, similar schools were organized.

Early in the 19th century a proprietary medical school was established in Baltimore. With this development, proprietary medical schools multiplied in the United States without restraint, for they were not limited by the number of educational institutions with which they might be affiliated. Their establishment represented a harmful precedent because, unlike such schools in London, they conferred degrees and gave the right to practice. Flexner, in his classic study,[1] reported that the United States and Canada in a little more than a century produced 457 medical schools—many, fortunately, short-lived. These schools were a financial boon to their proprietors and a scourge to the public because the doctors they turned out were mostly ignorant and incompetent.

In Utah one brief attempt to found a proprietary medical college was made in 1880 by a Dr. Frederick S. Kohler in a small farming village, Morgan City, some 40 miles northeast of Salt Lake City.[2] Four students graduated in 1882, but the college soon succumbed to the accusation that it was a "diploma mill." This left the way clear for the establishment of a medical school by the University of Utah shortly after the turn of the century.

The formation of a medical school at the University of Utah was a natural development in an institution tied closely to a church that traditionally fostered education. There had been a growing interest in the natural sciences and, on the part of some citizens, an increasing perception that more needed to be done to improve health care. There was also no doubt a desire on the part of prospective students and their parents to obtain medical education nearer to home and thus to avoid the expense of traveling East.

Early Attitudes and Obstacles

Medicine, however, was not wholeheartedly accepted by all adherents of the church. For example, Brigham Young is quoted as saying, "When I lay hands on the sick, I expect the healing power and influence of God to pass through me to the patient, and the disease to give way. I do not say I heal everybody I lay hands on, but many have been healed under my administration."[3] This, one must say, at least did no harm and had the merit of avoiding some of the harmful practices and medications that were then being promoted. Furthermore, it did not inhibit people from trying to help themselves.

The suspicion with which medicine was regarded by many was greatly influenced by the experience of the residents of Utah, Mormon and Gentile, with the practitioners of medicine who had ventured, for one reason or another, to this remote

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ABBREVIATIONS USED IN TEXT

AAMC = Association of American Medical Colleges
OSRD = Office of Scientific Research and Development
USPHS = US Public Health Service
VA = Veterans Administration

area of the country. These experiences had often been unhappy ones. In many parts of the United States, medicine at the turn of the century was primitive in many respects, and medical education was likewise very imperfect. That even graduates of authentic medical schools were at times referred to as "poison doctors" is understandable. We know that the practices of purging and venesection were responsible for many deaths; moreover, some of the drugs employed—for example, arsenic—were poisonous and physicians frequently carried infection from one patient to another. All in all, there was a basis for the distrust in which doctors were held. Despite the doubts, a number of Mormons went East to train at established medical schools and returned home to practice medicine and surgery.

In addition to these considerations, there was the problem of cost of establishing and maintaining a medical school and the fact that there were many demands on the limited resources of the community. What might be considered as a beginning was made by Dr. John Rockey Park, the first president ("principal") of the University of Utah, who set up classes for the teaching of biologic subjects in 1869.[4] Dr. Park was himself a doctor of medicine but abandoned his profession after three years of practice in Ohio when he decided to go West. He was a Gentile and a teacher at heart but not much progress was made until President Talmage took office in 1894. Talmage had a background in biology and biology expanded appropriately. With the arrival in 1904 of Ralph V. Chamberlin, PhD, from Cornell as assistant professor of natural history, education in biologic sciences was greatly stimulated. Over the next two years, Dr. Chamberlin organized and expanded the Department of Biology, establishing courses in vertebrate histology and embryology and, ultimately, in physiology and bacteriology. Soon a separate Department of Anatomy and Pathology was formed under Dr. Ephraim Gowans, who was shortly succeeded by Dr. John Sundwall.

A Two-Year Medical School

It is to Professor Chamberlin that credit should be given for starting medical training in the University of Utah. He was acquainted with the two-year medical course offered at Cornell and thought that a similar school could be set up in Utah, arguing that there was a need for better-trained physicians who could displace the existing quackery. He also recognized the need for the teaching of basic sciences by persons trained in these fields rather than by practitioners for whom such teaching was a side issue. He also emphasized that "high-grade teaching in the sciences and research work are inseparable."[5(p193)] Dr. Chamberlin also stressed the value of high standards, both for the state and for the profession, and felt that these could be best attained when the commonwealth supported such training, rather than leaving it to proprietary medical schools.

As a consequence of his efforts, a two-year medical school was officially established by the university administration in August 1905. And, to comply with state laws regarding accreditation, medicine was separated from biology. However, the medical school was officially made a department rather than a school, primarily as a concession to Dr. C. G. Plummer, a member of the university's Board of Regents, who felt that a medical school would be "too expensive," a refrain, incidentally, that one heard in 1943 and continued to hear for a number of years thereafter. It was not easy to convince people that Utah could not afford to continue to suffer from mediocre medical care, which was in the end more costly than first-rate medical education and health care.

Dr. Chamberlin was made dean of the school in April 1906, as well as professor of histology and embryology. Additional space was acquired, courses were added and 47 students were enrolled. The University of Utah's medical school thus joined eight other schools in the United States that offered a two-year course. As the result of an official inspection in the spring of 1906, the school was given an A rating by the Association of American Medical Colleges (AAMC),[4(p260),5(p193)] which made it possible for students to transfer with full credit to four-year schools.

Dean Chamberlin went on to plan the addition of the third year of a four-year course. The acquisition of the Judge Memorial Building near the university campus, which had been modified to

serve as a miners' hospital and home, would have provided an opportunity for some of the clinical training he envisioned. This idea was said to have the support of the "downtown" physicians, but at the university all was not smooth sailing. Pettiness and jealousy were strong forces. The potential growth of the medical school aroused the concern of the School of Arts and Sciences, especially of its dean, Byron Cummings. His strong opposition culminated in the shelving of the plan, the resignation in 1907 of Dean Chamberlin and the incorporation of the Department of Medicine in the School of Arts and Sciences. The university catalogue for 1907-1908 lists Byron Cummings, AM, as Dean of the Department of Medicine, a position he held until 1912-1913, when the arrangement was quietly abandoned as the result of repeated objections of visiting committees of inspection and accreditation.

Dr. Chamberlin, however, had laid a good foundation. For example, guided by the laws of other states, he presented to the Utah state legislature a bill providing cadavers for the school, which was approved in 1907[5(p203)] and has operated unchanged since that time. In the Flexner report on *Medical Education in the United States and Canada*[1] published in 1910, the Utah "half-school," as it was called, was described as having an attendance of 18, a teaching staff of six professors and ten of other grade, a budget of $10,000 and laboratories "adequately equipped for the routine instruction of small classes" in the traditional basic sciences of medicine.[1(p313)] The spirit was described as excellent. More liberal support was recommended, however, if the department was to justify its high entrance standards. It should be noted that Utah at that time had a population of 336,112, of which Salt Lake City accounted for 65,464.

At first the entrance requirement to the "Department of Medicine" was only a high-school course, but in 1909 a year of college work was added and, beginning in 1910-1911, two years of premedical work were required. Because of this, in 1910 Utah was again rated A by the AAMC and was listed among the top group of the 155 medical schools in the United States and Canada, becoming one of 16 schools in that category.

This happy situation was destined not to last. Dissension at the University regarding matters of salary and of personalities and other controversies led to resignations and recriminations, even demands for the removal of the president. As a result, the spirit of the medical school dropped to an all-time low that was to last seven or eight years. In the spring of 1916 the Board of Regents accepted President John A. Widtsoe's recommendation that the medical school be continued, providing the cost of its maintenance in the class A category did not exceed the then cost of its existence by $2,500 (Minutes of the Board of Regents, University of Utah, June 1, 1916 [unpublished]). This nominal (and reluctant?) show of support had little effect, however, because of the beginning of World War I. Ultimately, the ever-threatening possibility of a drop in rating to B (the category of the lower 37 of the 104 medical schools recognized at that time), the end of World War I and the appointment of George Thomas as president of the university in 1922 culminated in a slow uphill climb in educational standards and improvement in faculty and in curriculum. By 1922 Utah students were at least having less difficulty than before in transferring for their final two years to schools of high quality.

The Four-Year School

As time went on Utah students again found it difficult to transfer to four-year schools, this time mainly because the latter had to accommodate their own students. The AAMC urged that Utah become a four-year school, as did Ralph O. Porter, professor of pharmacology, who was appointed dean in 1923. Dean Porter began to raise standards and improve the faculty, something he accomplished only by producing some hard feelings.[3] The premedical requirement was raised to three years. In the end President Thomas, caught in the squeeze of the Great Depression, took a position opposed to the idea of a four-year school, an attitude heartily supported by the deans of other schools on the campus. From their viewpoint, the medical school was a threat to their budgets. The prospect of a minimum cost of $135,000 a year to operate a four-year school was too great a stumbling block. Furthermore, they strongly objected to the notion of salaries for professors in the medical school that would exceed their own.

Yet, pressure for a four-year school persisted. To improve the quality of teaching in the first two years, clinical experience was needed. Also, there was a genuine growing need for physicians. The Medical School Alumni Association, formed in 1935 and comprised of graduates of the two-year school, favored the formation of a four-year

school, as did the then dean, Lyman L. Daines, and the Utah State Medical Association. But the Board of Regents and the general public continued to demur.

Not until the retirement of President Thomas in November 1941 and the appointment of President Leroy E. Cowles did the atmosphere change. A committee of the Board of Regents (consisting of L. E. Viko, A. H. Reiser, W. H. Leigh and E. J. Glade) was formed and, with their recommendation and that of Dr. H. G. Weiskotten of the American Medical Association, plans were drawn up for the formation of a four-year medical school. Approval was given by the Board of Regents on May 18, 1942. Dr. A. Cyril Callister, a practicing surgeon, was appointed dean, half-time, with Professor Clay Freudenberger, acting dean following the death of Dr. Daines, as associate dean.

Although he was ultimately the subject of much criticism, the appointment of Dr. Callister as dean was fortunate. Much needed to be accomplished and Dr. Callister had the requisite firm and determined hand. Moreover, he was a graduate of Harvard, as well as an excellent salesman. One of his former classmates at Harvard was Dr. Alan Gregg, who by this time was Director of the Rockefeller Foundation for Medical Education and the person best informed about potential staff and overall approaches and objectives. Another important friend was Dr. Irving McQuarrie, head of pediatrics at the University of Minnesota. With their advice and help, by September 1943 the heads of the Departments of Surgery (Phillip B. Price), Obstetrics and Gynecology (A. Louis Dipple), Pediatrics (John Anderson) and Medicine (Maxwell M. Wintrobe) were on hand, recruited from Johns Hopkins Medical School and the University of Minnesota. Their offices and laboratories were established at the Salt Lake County General Hospital (see Figure 1), some four or five miles from the medical school building (Figure 2) on the University of Utah campus. Dr. H. L. Marshall, long associated with the

Figure 1.—The Salt Lake County General Hospital. The building shown housed mainly the surgical wards an offices, as well as the operating rooms and laboratories. In 1943, only three floors existed. The structure on th fourth floor and the extension to the right were added later. A former infirmary building (not shown) was used, i part, for medicine and pediatrics, as well as the heart station and some research laboratories. Obstetrics was i another one-story wooden "temporary" structure.

university in the Department of Physical Education, became Professor of Public Health and Preventive Medicine.

Overcoming Opposition

The situation these men encountered was not a rosy one. The university had reached an agreement with the Salt Lake County commissioners to turn over the clinical operation of the county hospital to the teaching staff so that it could be used as the teaching hospital. For its part, the medical school would give complete care to patients without cost to the county. This facility, however, was a striking contrast to the institutions from which they had come, and turned out to be much worse than any of them had expected. The hospital was dirty and poorly staffed, and it soon became apparent that its condition could not be readily improved. The hospital was a political plum and the county commissioner, who was in charge of "charities," staffed it with his henchmen and hangers-on. The superintendent, the management personnel, the kitchen staff, the dishwashers, the cleaning staff, the laundry staff, everyone was beholden to the commissioner and very few, if any, were interested in doing their job well. A drunken orderly might be discharged one day, only to return the next on the order of the commissioner. Everyone, even the nurses, was forced to contribute to the political fund. Only with great difficulty were the new clinical heads of the hospital ultimately able to exempt the nurses from this requirement. Almost comically (were it not so sad for the patients), when an election resulted in a change from one political party to another, the entire staff would be changed and the result would be total chaos.

The county hospital and its operation presented a continuing problem, one that was not improved to any important degree until after an accreditation crisis in 1954. This, as will be mentioned later, caused the county commissioners to agree to the appointment of a citizens' advisory board, made up of some of the business leaders in the community. These men could appreciate the problems of the hospital when they were explained by the clinical department heads. The county commissioners, though unimpressed by the hospital's department heads, recognized that their political careers could be seriously influenced by the opinions of the business leaders. From the time of the appointment of this board, the situation became more tolerable.

When the newly established four-year school was inspected with a view to accreditation in February 1944 by Dr. Fred C. Zappfe of the Association of American Medical Colleges and Dr. Victor Johnson representing the Council on Medi-

Figure 2.—The University of Utah Medical School building in the early days of the four-year school. Behind it is one of the temporary wood structures which were made available as more space was needed. These remained "temporary" until 1965.

cal Education of the American Medical Association, the need for changes and improvements in the basic science departments was evident. The content and the quality of the teaching had fallen far behind that of the better institutions in the United States. The immediate removal or demotion of several professors, some of long standing, was recommended. When this was attempted, however, charges of personal prejudice, authoritarianism and lack of appreciation of loyal service were made and there was much hard feeling. The administrative council of the university, on which sat some friends of those who had been criticized in the Zappfe-Johnson report, took their part. The council was concerned, moreover, that tenure was in jeopardy. Some members of the council were unwilling to admit that they were not qualified to judge the competence of those criticized, the needs of the curriculum or the qualifications of those newly recruited. They were upset, moreover, that the new department heads were to be paid $8,000 a year, in contrast to the $4,500 that was the top salary at the university. They could not be convinced that ultimately this would raise salaries in general at the university, as it later did.

There also was fear on the part of some of the "downtown physicians" that the medical school would flood the state with doctors and that the medical faculty would compete with them. Leaks of the Zappfe-Johnson report to the press added fuel to the crisis that developed and were supplemented by statements to the press by disgruntled persons. The full Zappfe-Johnson report had been withheld in the hope of shielding those who had been criticized. Eventually the whole report was exposed despite the unflattering comments it contained. Even the Association of University Professors was brought into the foray. The year 1944 was, indeed, exciting. Dean Callister was one of those severely criticized. Fortunately he stood his ground and continued to receive the loyal support of Dr. Louis E. Viko, a member of the Board of Regents and an outstanding and highly respected physician, and of Dr. Leo Marshall. In the view of the new faculty these were the "three horsemen."

Although beleaguered on all sides the Board of Regents continued to support the dean and the recommendations of the inspecting committee. Resignations followed and plans were made to revitalize and modernize the outdated and inadequate preclinical departments by securing outstanding persons to head them. As a result, conditional approval of the school was given at a second inspection in May 1944.

It soon became evident that one of the tasks of the new clinical department heads, in association with the dean, was the development of a medical school of which everyone, the university and the community alike, could be proud. Dean Callister was a headstrong person and preferred to rule with an iron hand. However, the new faculty were more experienced in the task at hand, having served in full-time teaching and research positions in some of the best schools in the country. There were clashes but decisions were eventually reached that all knew were in the best interests of the school. Drawing on their acquaintance with medical scientists throughout the country and with the advice of such men as Alan Gregg, the dean and the four new clinical heads recruited new department heads from the country's outstanding institutions for pharmacology, biochemistry, physiology and pathology.

With the resignation of Dr. Callister in January 1945 and the appointment initially of an interim dean's committee and in September 1945 of Dr. Leo Marshall as acting dean, the executive committee of the College of Medicine, made up of the heads of all the departments, became all-powerful, with the dean acting as its executive officer. This method of operation, incidentally, was continued for at least 20 years, and gave way only gradually to the assumption of more authority by the dean as the executive committee expanded and consequently became unwieldy.

What Utah Had to Offer

An important characteristic of the faculty of the new school was their willingness to try to build something worthwhile despite the absence of substantial resources. They realized that what Utah was offering was an *opportunity,* nothing more. Salt Lake City was the logical location for a new medical school. There was no school between the Canadian and Mexican borders on the north and south, or between Denver and the Pacific coast, where Portland had one medical school, Los Angeles two and San Francisco two. The budget available to recruit faculty was very small but Utah's tax base, with a population of about 600,000, was likewise small. The physical facilities were limited but the country was now in the throes of World War II. Like the pioneers who had preceded them in other ventures in the West, they

resolved to do their utmost with the resources that were available.

The members of the new staff were all relatively young. Their careers lay in the future, not behind them. Energy and drive were in abundance and the challenge was appealing. So also was the geographic location of Salt Lake City, with its magnificent outdoor attractions available summer and winter. Nowhere in the world is excellent skiing as easily accessible as in Salt Lake City and this fact alone contributed in no small part to recruitment and the esprit de corps that developed. It made up to some extent for the lack of cultural facilities. Of those who came in the first contingent, only one, the head of the Department of Obstetrics and Gynecology, soon left but he was promptly replaced by another excellent man, Dr. Charles McLennan.

Challenges and problems were in abundant supply. Despite the contention of many of the citizens of Utah, standards of education in the high schools and even at the university compared unfavorably with those the new faculty had noted elsewhere. Medical students had to be convinced that excellence was the goal and that they had to extend themselves to the utmost of their abilities. Demands were made on them to which they had not been accustomed, causing a few to succumb under such pressure. There was a complaint that the failure rate at Utah was as high as 10 percent, as compared with only 2 percent or 3 percent elsewhere. Nevertheless, though some students and perhaps some parents grumbled, most appreciated the efforts of the faculty and gave their best.

Antagonism on the part of some of the medical profession was fomented by those who had envisioned themselves as department heads or, at least, as professors, notwithstanding their lack of qualifications for such positions. Others perhaps feared competition by the new faculty, as already mentioned, and still others may have been discomfited by the gradual rise in the expectations of the public regarding the quality of health care. However, most physicians and surgeons of the community backed the school and the efforts of the faculty and were not worried by these changes.

The faculty was full time. They had not come to earn a fortune and the clinical staff readily agreed to see patients only on referral by other physicians and to limit their clinical work to the county hospital, with neither offices nor hospital staff appointments elsewhere. This practice limited the number of patients they could see and avoided competition with physicians in private practice. Furthermore, it left more time for teaching and research.

Support for Research

The faculty realized that one of the functions of a university, of which they felt the medical school to be an integral part, is to contribute to knowledge. Everyone expected to do research. Most of the new faculty had already pursued this objective and were dedicated to continue. A limiting factor, however, was the need for funds to develop laboratories and to hire technical personnel. This presented a very real difficulty because the state legislature and the university, with their lingering doubt that Utah could "afford" a four-year medical school, were unlikely sources for such help. Here private gifts, though relatively small in terms of the 1980's, played an exceedingly important role. Dr. Wintrobe, who had been conducting experiments at Johns Hopkins in which pigs were used, would not come to Utah unless facilities could be provided to continue these studies. To accommodate his needs, the very persuasive Dean Callister secured over $30,000 from Morris and Joseph Rosenblatt of the EIMCO Corporation. Morning Milk Company gave $10,000 for the pediatric department and the LDS Church followed with $25,000 for remodeling and equipping the pharmacology department, thereby making it possible to recruit Dr. Louis Goodman. And then there was a fortunate turn of events.

World War II was ending and the US government was searching for a way to continue to support research. Under the Office of Scientific Research and Development (OSRD), research had been undertaken during the war that obviously would be important for civilians and the military. Luckily, Senator Elbert Thomas of Utah was the chairman of the committee assigned this task. Unaware of the government's interest, the new head of the Department of Medicine was looking for an area of research, indigenous to Utah, in which some of his staff might become interested, and he was seeking funds to support such studies. He had learned that observations on a hereditary form of muscular dystrophy were being conducted by a practicing orthopedist, Dr. Samuel H. Baldwin, and a geneticist at the university, Dr. Fayette Stephens. These men had limited training for an in-depth study of such a problem, and no financial support. But the conditions were ideal. Mormon

polygamy, intermarriage and inbreeding and the stability of the population made Utah unique for the study of an hereditary disorder. With the enthusiastic support of Drs. Stephens and Baldwin, plans were made to join with them and to expand the studies. Informed of this, Dr. Leo Marshall, a close friend of Senator Thomas and an enthusiastic supporter and promoter of the four-year school, communicated with the senator. The latter, along with Surgeon-General Parran of the US Public Health Service (USPHS), encouraged Dr. Wintrobe to draw up a comprehensive program of research and ultimately application was made for a research grant of $100,000 per annum for the study of muscular dystrophy and other hereditary and metabolic disorders. The project was deliberately made very broad.

The grant request arrived in Washington at a crucial time. A specific request was needed to initiate the broad research grants program that Senator Thomas and Surgeon-General Parran were planning. The Utah request was incorporated into the bill that established the USPHS Research Grants Division and was numbered A-2.

To what the number A-1 applied has not been discovered, but probably it referred to the fact that of the $100,000 approved by Congress, $8,000 was withheld, with the full agreement of the applicant, to establish the office in Washington of the Research Grants Division of the USPHS. Utah thus received $92,000, a sum that proved to be a particular boon for the Departments of Medicine, Biochemistry and Physiology, for they were able to recruit additional staff and to develop badly needed research facilities. The grant subsequently was renewed each year for 23 years and brought to Utah a total of $4,043,689. Moreover, it served as the nucleus for many other studies that in time became the subjects of additional research grants. The outcome of the various investigations supported by the USPHS through its program of research support, with help from various foundations and private sources, has brought international recognition and renown to the university and its staff.

The early successes in developing facilities for research, even though the latter were limited, and the fortunate turn of events as regards government funding, served to breed optimism among the faculty and this, in turn, helped greatly in further recruitment. Dr. Thomas Dougherty came from Yale to head the Department of Anatomy, as did Dr. Horace Davenport to head the Department of Physiology.

Veterans Administration Hospital

On the clinical side, Utah again showed itself to be a pioneer. The quality of medical care in the hospitals of the Veterans Administration (VA) had been gradually changing for the worse. Realizing this, Dr. Magnusson, the administrator of the system, decided to try to interest the medical schools of the country in assuming supervision of the hospitals in their vicinity. For many medical schools, this would represent a burden. For Utah, with only the Salt Lake County Hospital as its clinical base, the Salt Lake VA Hospital represented a welcome opportunity. The heads of the Departments of Medicine and Surgery stated that they would be happy to undertake the supervision of patient care at the VA Hospital, provided that they would be allowed not only to recruit and supervise the house staff for the hospital, but also to send third- and fourth-year students there.

The last request, however, was contrary to federal regulations. Veterans could not be exposed to students—only to inferior medical staffs. Fortunately Dr. Magnusson, who was aware of the advantages of strong teaching programs and the resulting superior patient care in university hospitals, indicated that he did not need to be familiarized with all the details. The result was that the University of Utah became the first school to use a VA hospital in its teaching program, a practice that, because of its success, ultimately was officially sanctioned.

In the meantime, the conditions at the County Hospital had become almost intolerable. The political control of its administration and operation had continued. The James A. Hamilton Associates, hospital consultants from Minneapolis, were invited to make a study and their report was devastating.[6] Loss of accreditation by the American Medical Association became a serious possibility, one that would be harmful to the university, the medical school and the hospital. Charges and recriminations once again created a crisis atmosphere. Accreditation actually was withdrawn briefly and the county commissioners agreed to select a trained hospital administrator from a list agreed on by the university and the commissioners. Equally important was the appointment of a citizens' advisory board, as mentioned earlier.

The threatened loss of hospital accreditation was thereby averted.

Medical Center

The building of a medical center on the university campus, promised in 1943, was realized in 1965, albeit piecemeal. First, a cancer research wing was erected in 1951, mainly through federal funding. Then a radiobiology unit was added with Atomic Energy Commission funding. In the meantime, construction of a new VA hospital on adjoining US Army Fort Douglas property was begun. For a while, differences of opinion regarding the best site for a university hospital, adjoining the county hospital in the center of the city or in a more remote location in the eastern area of the university campus, threatened progress. Furthermore, the Utah state legislature continued to be an uncertain source of support. The possibility of federal matching funds served to stimulate their interest and that of the university, and in 1955 the Board of Regents finally approved plans for a medical center. A campaign to secure financial support from private sources was approved by them in 1958. The story of how support and funds were ultimately secured so that the medical center, opened in 1965, came to be constructed for the comparatively small sum of $14,500,000 is one of patience, generosity and determination on the part of many persons, including medical school faculty and administrators, a few university administrators, a number of the members of the Utah medical profession, a few legislators and a significant number of forward-looking, public-spirited Utah citizens.

The subsequent history of medical education in Utah is a story of the development and the outstanding accomplishments of each of the many departments of the school and of the various members of the faculty—the development of additional units, the East Wing, the Eccles Library and, in 1981, a magnificent addition to the clinical center and the seven-story Medical Research and Education Building (see Figure 3). The latter two constructions were at a cost approximately four times that of the structure opened in 1965. Private gifts, including contributions by members of the community and the medical fac-

Figure 3.—The University of Utah Medical Center in 1981. In the foreground is the new clinical facility. Behind it, and attached to it, is the Medical Center built in 1965 which then provided clinical facilities, laboratories and offices. The tallest building to the left is the new Medical Research and Education Building and far beyond it, two buildings for student housing. Hidden by the Wintrobe Research Tower (Research and Education Building) is the Spencer Eccles Health Sciences Library and beyond these are the College of Nursing and the College of Pharmacy.

ulty, and funds provided by the State of Utah and the US government, made these developments possible. These facilities gradually replaced the various temporary structures that were put to use as necessity required: a latrine that formed part of the first metabolic laboratory where the earliest biochemical investigations on muscular dystrophy and other hereditary and metabolic disorders were carried out, the "blood shed" into which hematologic research expanded, a former military stable and a number of other ramshackle "make-dos" whose temporary status stretched to many years.

The growth of the medical school fortunately has not been parallel to that of the population of the state. Whereas the population of Utah did not quite triple between 1940 and 1980, the budget of the College of Medicine has grown from $150,000 in 1943-1944 to approximately $45 million for 1981-1982, a 300-fold increase. Classes have increased in size from 35 to 100 and the total enrollment of medical undergraduate students has risen from 160 in 1944 to 403 in 1981. The number of graduate students has grown from 8 or 10 to 480, if one includes residents and fellows as well as masters' degree and PhD candidates.

The makeup of the greatly expanded budget is worth reviewing. Of the $45 million, $8.4 million comes from the state, $1.8 million from student fees, approximately $19 million from the US government in the way of research grants, $3.5 million from private sources (mostly foundations and corporations—almost all from outside of Utah), $10.5 million from earnings by full-time staff physicians and turned back to the school and the remainder from miscellaneous sources. The impact of this infusion of funds, more than five times the amount provided by the state, on the economy of Utah is worthy of reflection. One more statistic of significance is that in 1944 the University of Utah received a total of $9,800 in research funds. In 1981, $60,170,857 were received for the support of research. Of this amount, 42.7 percent was awarded to the College of Medicine. Can Utah now repeat the old refrain, "We can't afford a medical school"?

Summary

Throughout, the guiding principles and goals of the medical school have been excellence in teaching, excellence in patient care and excellence in research. Every member of the faculty has contributed to these goals, each in his own way. The establishment of US government financial support of medical research after World War II proved particularly important for Utah. Without such a start, it would have been extremely difficult to secure sufficient funds from private sources and none could have been expected from the State of Utah. As to private gifts, except for those provided by a few generous and farseeing citizens, it was necessary for the faculty to prove their worth before much local support could be stimulated. As it turned out, by enlisting as members of the faculty of the four-year medical school a number of able, hard-driving, imaginative and ambitious young medical scientists, many applications for research grants were approved by the USPHS and by various foundations, pharmaceutical houses and other organizations. The success of these studies led to recognition of the University of Utah as an important medical research center. With successful research and a growing reputation as an educational center, private contributions became less and less difficult to obtain and the state legislature became more generous. Furthermore, the principle was established that every member of the faculty was expected to teach and to carry out research and, in the case of the clinical faculty, to participate in clinical care. As a consequence, the acquiring of research funds made it possible to secure a well-rounded faculty that contributed to all the various aspects of a modern medical center and teaching and research institution. The result has been that the standards of teaching and patient care, in addition to research, have attained a very high level. In time, the University of Utah College of Medicine has come to be known as one of the important medical centers of the United States and is internationally recognized for its research contributions, as a postgraduate training center and as the source of several important medical textbooks that are used throughout the world.

REFERENCES

1. Flexner A: Medical Education in the United States and Canada. New York, Heritage Press, 1973 (reissue of the 1910 report)

2. Fitzpatrick WK: Medical memorabilia—Utah's first medical school. Rocky Mt Med J 1971 Jan; 68:21

3. Young WB, quoted in A History of the University of Utah College of Medicine, thesis for medical doctorate, Leslie R. C. Agnew, MD, Mar 29, 1963 (unpublished)

4. Chamberlin RV: The University of Utah, a History of the First Hundred Years, 1850 to 1950. Salt Lake City, University of Utah Press, 1960

5. Chamberlin RV: Life Sciences at the University of Utah, Background and History. Salt Lake City, University of Utah Press, 1950

6. Hamilton JA and Associates: The Hamilton Report, Confidential report, 2 Vol. Minneapolis, James A. Hamilton and Associates, Oct. 29, 1954

Refer to: Watts MSM: Rising health care costs (Medicine in Perspective). West J Med 1982 Apr; 136:367-368

Rising Health Care Costs

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EDITOR'S NOTE: *The following is an editorial reprinted in its entirety from the November 1968 issue of* CALIFORNIA MEDICINE *(the immediate predecessor of* THE WESTERN JOURNAL OF MEDICINE*). Although there have been much rhetoric and not a few initiatives to control the cost of health care, the "national commitment to make a greater number of more sophisticated and expensive services available to a greater number of better informed and more demanding people" appears not to have changed, and one can suspect it will be difficult, if not impossible, for this to change, even though the "Manhattan Project" approach may now have become obsolete.*

—MSMW

HEALTH CARE COSTS are rising. Quite properly this is being viewed with concern, and sometimes alarm, by government, labor and the public who of course must ultimately pay these costs. Physicians, hospital administrators and others in the health care industry are also and properly disturbed. As might be expected, there is a natural tendency to blame this unpopular state of affairs on someone or something which can be made a scapegoat. There have been allegations and accusations against money-mad physicians, uneconomic hospital practices, inefficient health care delivery systems, unnecessary and excessive union wage increases, and unreasonable demands and expectations on the part of government or the public. A convenient catch-all is inflation, to which almost everyone gives some of the blame. But no one of these scapegoats, nor even all of them together, can account adequately for the rising health care costs. The true cause is far more basic and far less often given its due.

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It is suggested that the major rise in health care costs can be traced back to a philosophy engendered by the very expensive but very successful Manhattan Project of World War II. This philosophy states that almost anything can be accomplished if one is willing to spend enough money to get it done. World War II promptly terminated when the atomic bomb became available and was used. The money spent on the Manhattan Project achieved its purpose. A scientific and technologic miracle had been accomplished.

The principle was next applied on a large scale in medical research with the expectation that if enough money were spent, scientific and technologic miracles could also be worked in this field—and this time for the betterment of mankind. Vast sums were contributed from both public and private sources, research thrived, and there were many impressive results. Progress in medical science was dramatic and it was also very well dramatized. The prospect of better health for all was clearly on the horizon for everyone to see and the public responded with expectations followed by increasing demands until health and health care are now generally accepted as human rights somehow to be guaranteed by society. But not yet settled is just how this is to be done, what the cost will be, or how it is to be paid for.

As might be expected the principle of the Manhattan Project is once again being applied in the hope that another scientific and technologic miracle can be achieved. Vast sums of money are being pumped into the health care system, again from both public and private sources. The government's focus has been particularly upon the removal of any significant financial barriers to the health care of the aged and the indigent of any age, and to make sure that this care is rendered to all with equal dignity and within the mainstream of good

medical practice. It may be expected that substantial funding will soon become available for manpower procurement and training, for better deployment of knowledge and skills, for equipment and facilities, and for planning regional and community health services. The non-governmental focus has been to develop better programs, quality standards and utilization control within the private sector. The emphasis has been upon accomplishing all this by strengthening the vital pluralistic system which has characterized health care in this nation and encouraging it to plan and experiment to find better and more efficient answers. This is as it should be.

It would seem then that the basic cause of the enormous rise in the amount of money being spent on health care is simply a national decision to spend more money to bring more sophisticated health services to many more people and to do this on a grand scale on the theory that almost anything can be accomplished if one is willing to spend enough money to do it. This does not say that such things as inflation, increases in wages, salaries, fees, cost of living and cost of working, supplies, equipment, facilities and operating overhead do not contribute to these rising costs. But it does suggest that allegations and accusations will do little to help, and that while improvements in economic efficiency and productivity must be sought and put to use, these will by no means be sufficient to control the rising costs of health care. As long as there is a national commitment to make a greater number of more sophisticated and expensive services available to a greater number of better informed and more demanding people, and as long as both the public and the private sector are willing to spend more and more to do this, the amount of money spent on health care will inevitably increase, and thus the costs will continue to rise by any measure and in spite of whatever rhetoric is used. It is time this basic fact is recognized and accepted for what it is by all concerned.

Refer to: Denson TA, Manning PR: Current problems in medical practice as viewed by California physicians (Information). West J Med 1982 Apr; 136:369-372

Information

Current Problems in Medical Practice

As Viewed by California Physicians

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THE CENTRAL MISSION of medicine, to prevent and cure disease and to reduce human suffering, rests on accurate diagnosis, effective therapy, a good doctor-patient relationship, public health measures and the competence of all health-care personnel. As scientific advances, governmental regulations and social policies make patient care more complex, problems emerge that must be continually scrutinized if we are to provide optimal medical care. Accordingly, we asked a group of physicians to rank the most serious problems encountered in their practice.

Methods

The Instrument

To design a survey instrument for this purpose with the least bias, we first used an open-ended approach in which 179 physicians attending postgraduate courses sponsored by the University of Southern California gave free-form answers to the question: "What are the three most serious problems (both medical and nonmedical) in your practice?" From the answers collected, we created a simple questionnaire that would produce information in an assessable form by grouping the open-ended responses into 25 categories. The most serious problems stated by a second group of 98 physician attendees were similarly grouped into these 25 categories. Three physicians then cross-validated the placement of individual problems into the categories, with 72 percent agreement. The few problems that did not fit into the 25 categories were placed in a 26th and labeled "other."

The 26 categories were listed in a simple checklist which, together with the instructions, was pilot tested for clarity. The physicians were asked to rank the three most serious problems as 1, 2 or 3. After minor changes, the final version (see Figure 1) was arranged in a self-mailer format. The retest reliability of the questionnaire was examined among two separate groups of physicians, with 79 percent (n=89) agreement in problem selection over a five-day interval and 59 percent (n=41) agreement over a three-week interval.

Subjects

In 1980 the California Medical Association (CMA) had 24,865 active members representing 36 specialties and subspecialties. We selected 18 specialties and subspecialties with a combined membership of 18,583 physicians for our survey. Using membership lists in which CMA members were grouped by zip code within specialties, we took every fifth name for a total sample of 4,448 physicians, which we deemed representative of the membership's specialties and geographic distribution. (The sample size is not exactly one fifth of the membership because each specialty and subspecialty group was a separate sampling frame. These sampling frames varied in size, and a "random start" technique was used to select the sample.)

Of the physicians who received our questionnaire, 1,704 (39 percent) gave usable responses to the first mailing. A second mailing to those who did not respond increased the total number of usable responses to 2,745 (62 percent). Only 83 responses were deemed unusable because of failure to follow directions. Chi-square analyses showed the responding sample to be representative of both the specialties and the geographic distribution of California's physicians.

Analysis

We counted the number of respondents for each item chosen as one of the three most serious problems. The item chosen most frequently by the 2,745 respondents was then given a rank of 1, the next most frequently chosen was ranked 2

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and so forth through all 26 items. For example, "government regulation of medical practice" was cited as the most serious problem by 604 respondents, the second most serious by 464 respondents and the third most serious problem by 239 respondents, for a total of 1,307 citations. Based on this total the item ranked first among the 26 problems on the questionnaire.

We also calculated a weighted score for each item by multiplying the relative importance assigned to the item by the number of respondents assigning that level of importance to the item. The rankings resulting from this procedure had a correlation of rho = 0.992 with the simple frequency count. Since the two analyses correlated so highly, we report only the results of the frequency count, in the interest of simplicity.

Results

Table 1 shows the 26 problem categories listed in the order of their frequency. The rankings do not, of course, indicate the distance that the physicians perceive between any two of the items on any absolute scale of importance, but they do indicate what problems are considered most serious to this group of physicians in California.

Of the 86 problems in the "other" category (less than 1 percent of the total number of responses), the only items recurring with reasonable frequency were a physician surplus or patient

PROBLEMS IN PRACTICE

When asked to describe the major problems they face in practice, over 200 physicians have identified the problems listed below. Please read the list and decide upon the THREE MOST SIGNIFICANT PROBLEMS in your practice. In the space next to those three problems, write a "1" next to the most significant problem, a "2" next to the second most significant problem, and a "3" next to the third most significant problem. You may use the space below each item to describe details of the problems.

PLEASE RANK ONLY YOUR TOP THREE PROBLEMS. If one or more of your major problems does not fit into the categories, mark "OTHER" and briefly describe the problem in the space provided.

_____ Relationships with colleagues	_____ Patient compliance
_____ Practice coverage	_____ Concern for malpractice
_____ Non-M.D. health care professionals	_____ Negative influence of media on patients (TV, news, etc.)
_____ Hospital policies and/or hospital administration	_____ The telephone
_____ Regulatory agencies (JCAH, etc.)	_____ The demanding patient
_____ Third Party payers	_____ Patient education
_____ Government regulation of medical practice	_____ Legal and ethical issues
_____ Personnel selection/supervision	_____ Charts/record-keeping
_____ Paperwork	_____ Cost containment for the benefit of patients
_____ Financial management of practice	_____ Patient-related time commitments
_____ Diagnosis	_____ Personal time management
_____ Therapy	_____ Continuing medical education
_____ Doctor-Patient relationship	_____ OTHER: (Please describe)

Figure 1.—Questionnaire used in survey.

TABLE 1.—*Current Problems in Medical Practice as Seen by Physicians*

Rank	Number Reporting	Problem
1	1,307	Government regulation of medical practice
2	915	Paperwork
3	801	Concern for malpractice
4	673	Third-party payers
5	504	Regulatory agencies (including JCAH)
6	472	Cost containment for patient benefit
7	344	Personal time management
8	326	Hospital policies
9	324	Negative influence of media on patients
10	313	Financial management of practice
	* * *	
11	245	Charts and record keeping
12.5*	234	Personnel selection/supervision
12.5*	234	The telephone
14	220	The demanding patient
15	215	Patient-related time commitments
16	180	Non-MD health care professionals
17	165	Legal and ethical issues
18	162	Continuing medical education
19	144	Relationships with colleagues
20	136	Practice coverage
21	98	Patient compliance
22	79	Other (listed separately)
23	58	Patient education
24	43	Diagnosis
25	28	Therapy
26	21	Doctor-patient relationship

JCAH = Joint Commission on Accreditation of Hospitals

*Denotes tied ranks.

shortage in certain geographic areas or specialties (n = 16) and concerns about possible "competition between private physicians and HMO's" (n = 9).

Discussion

From previous studies, we expected that nonmedical problems such as administrative and organization problems would be mentioned more often than medical problems, even though the latter are central to the practice of medicine.[1,2] We were, however, startled at the relative infrequency of diagnosis, therapy and the doctor-patient relationship, the raison d'etre for medicine, which ranked 24, 25 and 26, respectively, among the 26 categories. In fact, only one item (cost containment for patient benefit) among the top ten mentioned is directly related to patient care. Nor did the ten most common problems include such items directly related to patient care as charts and record keeping, the demanding patient, patient education, or legal and ethical issues. On the surface at least, physicians seem to be most concerned with societal and governmental regulatory pressure and, to a lesser extent, with managing their time and relating to the medical establishment.

The 25 items undoubtedly were interpreted somewhat differently by different physicians, so strict reliance on our ranking from 1 to 26 is not warranted. Nevertheless, the magnitude of the frequency of selection of less direct aspects of patient care is so great in contrast to the infrequency of selection of "diagnosis, prescription and doctor-patient relationships" as to warrant considering several nonmedical problems to be distractions from, if not actual barriers to, optimal medical care.

The fact that the 2,745 physicians surveyed cited nonmedical aspects of practice much more often than "medical" problems raises several broad and significant questions:

- Do the time and concern that physicians spend on nonmedical problems significantly impede health care?
- Do nonmedical issues such as government regulations actually improve patient care and thus offset physicians' dissatisfaction with them?
- Do nonmedical issues predominate as problems because little or no attention is given them in medical school or continuing education?
- How can undergraduate and continuing education address the problems most often mentioned?

Optimists and pessimists may draw different conclusions from this study. Optimists may reason that diagnosis and therapy, the primary medical mission, are handled so effectively as not to cause serious concern. Pessimists may conclude that nonmedical problems in patient care have become so onerous and overwhelming that they distract physicians from their primary mission. Even though we favor the second conclusion, we remain surprised at the frequency with which the physicians mentioned nonmedical problems as serious difficulties in their practice. Until the questions we have raised are answered we must assume that the nonmedical problems are real and possibly harmful to patient care.

Summary

To determine the most serious problems in medical practice as viewed by physicians, we asked 2,745 members of the California Medical Association, "What are the most serious problems (medical and nonmedical) that you experience in practice?" The five most frequently stated prob-

lems (government regulations of medical practice, paperwork, concern for malpractice, third-party payers, regulatory agencies) were not directly related to the care of patients. Diagnosis, therapy and the doctor-patient relationship—the essential core of medical practice—ranked respectively 24, 25 and 26 in frequency among 26 categories. Physicians thus seem to be concerned primarily by nonmedical problems. The weight of these nonmedical problems in practice may be barriers to optimal patient care by distracting physicians from the performance of their primary mission.

REFERENCES

1. Brown CR Jr, Fleisher DS: The bi-cycle concept—Relating continuing education directly to patient care. N Engl J Med 1971 May 20; 284 (Supplement):88-97

2. Williamson JW, Alexander M, Miller GE: Continuing education and patient care research—Physician response to screening test results. JAMA 1967 Sep 18; 201:118-122

Refer to: Naeim F, Froetscher L, Hirschberg GG: Treatment of the chronic iliolumbar syndrome by infiltration of the iliolumbar ligament (Information). West J Med 1982 Apr; 136:372-374

Information

Treatment of the Chronic Iliolumbar Syndrome by Infiltration of the Iliolumbar Ligament

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THIS STUDY ATTEMPTS to establish the respective value of local infiltrations with lidocaine alone and lidocaine mixed with dextrose in the treatment of the chronic iliolumbar syndrome (ILS).

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This syndrome has been described as a distinct low back pain syndrome with typical unilateral findings of low back pain produced by the hip flexion test and the Patrick test.[1] There is also an exquisitely tender point at the posterior iliac crest. The chronic form of this syndrome responds very poorly to the common methods of treatment of low back pain such as rest, analgesics, heat and other forms of physical therapy, and it is frequently aggravated by pelvic traction. Whether or not the patient is treated, there are remissions and exacerbations which may continue for a lifetime. Many patients complain of a constant ache that is aggravated by prolonged sitting and standing. The onset frequently follows a lifting accident or a fall.

Most likely the chronic ILS is the result of soft tissue injuries to the iliolumbar ligament and constitutes the most common form of low back sprain. However, sometimes it is found to be associated with a radiculopathy and some authors believe that all backache is discogenic in origin. The clinical features have also been attributed to a facet syndrome in the lower dorsal area.[2] For this reason we prefer the word "syndrome" to "sprain."

Historical Review

Therapeutic Use of Local Anesthetics

As early as 1930, Leriche pointed out that after infiltration of a tender ligament or tendon with procaine there was not only temporary relief of discomfort but a more prolonged effect than what one would expect from the anesthesia. After repeated infiltrations of the painful tendon or ligament with procaine, Leriche actually reported complete recovery.[3] In the United States this method was first described by Steinbrocker.[4] Travell in numerous publications has reported relief of musculoskeletal pain in many areas of the body by the infiltration of "trigger points" with procaine.[5-7] Travell's explanation of this therapeutic effect is that the anesthetic breaks a chronic pain cycle. More recently Steinbrocker preferred the use of lidocaine because of its prolonged effect and lesser chance of allergic reaction.[8]

Therapeutic Use of Sclerosing Agents

The use of hypertonic dextrose is an outgrowth of the theory of musculoskeletal pain developed by Hackett.[9] This author postulates that the pain is caused by a microscopic tear in a ligament or

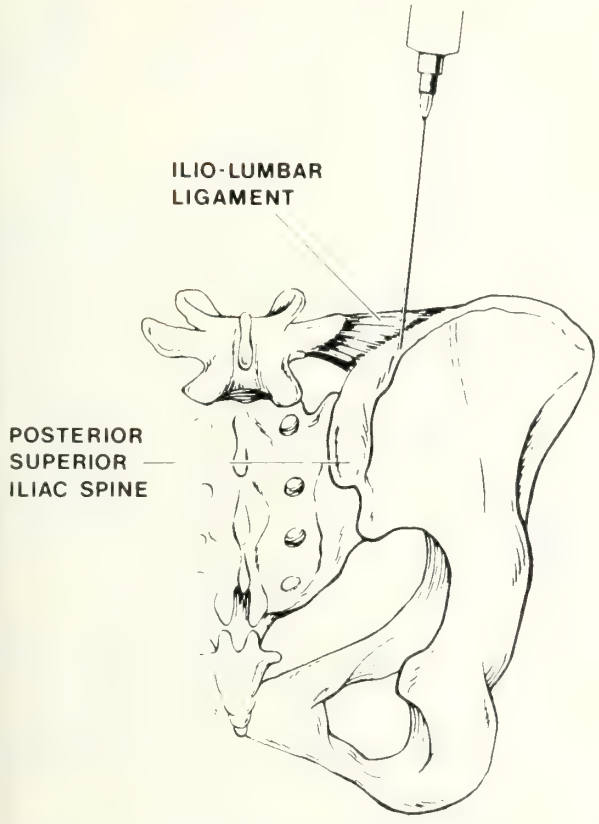

Figure 1.—Site of infiltration of the iliolumbar ligament. (Reproduced with permission from Hirschberg et al.[3])

tendon at the attachment to the bone. Repeated infiltrations of this area with a sclerosing agent cause acute inflammation followed by sclerosis which repairs the gap in the ligamentous or tendinous attachment. Lidocaine is added to avoid the pain caused by hypertonic dextrose. This method is used by only a small number of physicians.

Patients and Methods

Patients

The study involved patients with proved chronic iliolumbar syndrome. They had the chief complaint of low back pain that had lasted at least three months. The group consisted of 13 women and 3 men, and ranged in age from 19 to 80 years old. Nine patients were treated with lidocaine alone and seven with a mixture of lidocaine and dextrose. All patients had a diagnostic workup which consisted of a history, a complete general medical examination and a specific low back examination to determine the diagnosis of iliolumbar syndrome. They also had a radiologic assessment of the lumbosacral spine and laboratory

TABLE 1.—*Patients Treated With Lidocaine Only*

Patient	*Age*	*Sex*	*Duration of Pain (months)*	*Number of Treatments*	*Results*
1	32	♀	24	5	Good
2	53	♀	9	6	Good
3	25	♀	14	6	Poor
4	45	♀	9	6	Poor
5	42	♀	24	6	Poor
6	80	♀	36	4	Good
7	24	♂	14	6	Poor
8	55	♀	3	4	Good
9	58	♀	48	6	Poor

TABLE 2.—*Patients Treated With Lidocaine and Dextrose*

Patient	*Age*	*Sex*	*Duration of Pain (months)*	*Number of Treatments*	*Results*
1	63	♀	36	4	Good
2	53	♀	24	6	Good
3	36	♂	14	6	Good
4	28	♂	84	6	Poor
5	56	♀	8	6	Good
6	60	♀	36	6	Good
7	66	♀	60	6	Good

studies to rule out a systemic rheumatic disorder. Patients were included in this study if they had no clinical or laboratory evidence of a specific pathologic condition and the clinical findings consisted of unilateral low back pain that could be produced by the hip flexion and Patrick tests and that disappeared following infiltration of the appropriate iliac crest with lidocaine.

Technique of Treatment

The site of injection was the posterior iliac crest as shown in Figure 1. The patients in group 1 received 5 ml of 1 percent lidocaine solution while the patients in group 2 received a mixture consisting of 2½ ml of 2 percent lidocaine and 2½ ml of 50 percent dextrose solution. Five minutes following the injection the hip flexion and Patrick tests were repeated and found to be negative. This was done to verify the accuracy of the injection.

Evaluation of Results

The patients were evaluated at the end of the treatment period and again after six months by a member of the team who had not treated them. The results were rated "good" if the following criteria were met: (1) The patient claimed pronounced improvement. (2) The patient was able to carry out all activities of daily living with

minimal or no discomfort. (3) The patient required no pain medication for low back pain. (4) The tests for iliolumbar syndrome were negative.

The results were rated "poor" if one or more of the above criteria were not met.

Results

The results are presented in Tables 1 and 2. Of the nine patients who received lidocaine alone four had a good result. Of the seven patients who received lidocaine and dextrose all except one had a good result. Altogether 10 patients out of a total of 16 recovered.

Discussion

Considering the resistance of the chronic iliolumbar syndrome to treatment the total result of ten recoveries among 16 patients is encouraging. It shows that treatment by injection is superior to medication and physical therapy that these patients have had in the past. As to the relative merits of lidocaine alone as compared with lidocaine with dextrose the findings suggest a superiority of treatment with dextrose but a larger number of cases will be needed to provide definitive findings.

Unfortunately, treatment with dextrose has been discouraged for two reasons. Some physicians dispute its effectiveness, though no study to support this contention has been found by us. Furthermore, this treatment has been considered dangerous. Hackett originally used phenol to produce a sclerosing effect. Several accidents were reported resulting from injection of phenol into the subarachnoid space while the physician tried to infiltrate a spinal ligament.[10-12] This has led to a condemnation of Hackett's method as an unsafe procedure. To our knowledge no untoward effect has ever been reported when hypertonic dextrose is used as a sclerosing agent.

Summary

A total of 16 patients with chronic iliolumbar syndrome who had been symptomatic and disabled for three months or more were treated by a series of infiltrations of the iliolumbar ligament. Nine patients were treated with lidocaine alone and seven with lidocaine and dextrose. The overall response was a significant recovery in 10 patients out of 16. Six of the seven patients treated with lidocaine and dextrose recovered, but only four of the nine treated with lidocaine alone recovered. The potential risks of dextrose therapy are discussed.

REFERENCES

1. Hirschberg GG, Froetscher L, Naeim F: Iliolumbar syndrome as a common cause of low back pain: Diagnosis and prognosis. Arch Phys Med Rehabil 1979 Sep; 60:415-419

2. Maigne R: Low back pain of thoracolumbar origin. Arch Phys Med Rehabil 1980; 61:389-395

3. Leriche R: Des effets de l'anesthesie a la novocaine des ligaments et des insertions tendineuses peri-articulaires. Gazette des Hopitaux 1930; 73:1294

4. Steinbrocker O: Arthritis in Modern Practice. Philadelphia, WB Saunders Co, 1941

5. Travell J, Rinzler SH: The myofascial genesis of pain. Postgrad Med 1952; 11:425-434

6. Travell J, Rinzler SH, Herman M: Pain and disability of the shoulder and arm—Treatment by intramuscular infiltration of procaine hydrochloride. JAMA 1942; 120:417

7. Travell J, Travell W: Therapy of low back pain by manipulation and of referred pain in the lower extremity by procaine infiltration. Arch Phys Med 1946; 27:537-547

8. Steinbrocker O, Neustadt DH: Aspiration and Injection Therapy in Arthritis and Musculoskeletal Disorders. New York, Harper and Row, 1972

9. Hackett GS: Ligament and Tendon Relaxation Treated by Prolotherapy. Springfield, IL, Charles C Thomas, 1958

10. Hunt WE, Baird WC: Complications following injection of sclerosing agent to precipitate fibro-osseous proliferation. J Neurosurg 1961; 18:461-465

11. Keplinger JE, Bucy PC: Paraplegia from treatment with sclerosing agents. JAMA 1960; 173:1333-1335

12. Schneider RC, Williams JJ, Liss L: Fatality after injection of sclerosing agent to precipitate fibro-osseous proliferation. JAMA 1959; 170:1768-1772

THE NEVADA STATE MEDICAL ASSOCIATION PRESENTS

UPDATE: VASCULAR DISEASE 1982

SCIENTIFIC SESSION

Friday, May 14, 1982
MGM GRAND HOTEL, RENO

MGM GRAND HOTEL

ECredits: Approved for AMA Category 1, AAFP and CE Units for Nurses.
itration: 7:30 am - 8:00 am (coffee & rolls)

ome: Robert W. Clark, M.D., N.S.M.A. President
gam Chairman: Owen C. Peck, M.D.

am - 8:50 am **LARRY NOBLE, M.D.**, Asst. Professor of Internal Medicine, University of Nevada School of Medicine.
"NEWER DRUGS IN TREATMENT OF CARDIAC ARRHYTHMIAS"

am - 9:40 am **ROBERT S. ELIOT, M.D.**, Professor of Medicine, University of Nebraska School of Medicine;
"LIFESTYLE, BEHAVIOR AND STRESS IN CARDIOVASCULAR DISORDERS"

am - 11:00 am **JOHN E. CONTE, JR., M.D.**, Chief, Clinical and Infectious Disease, U.C. San Francisco School of Medicine.
"ENDOCARDITIS"

am - 11:50 am **GLENN A. LILLINGTON, M.D**, Chief, Pulmonary Disease, U.C. Davis Medical School.
"FIVE DISEASES CALLED PULMONARY EMBOLISM"

- 2:00 pm Luncheon
Guest Speaker: **ROBERT S. ELIOT, M.D.**
"MANAGEMENT OF 20TH CENTURY STRESS"

pm - 2:50 pm **JERRY R. MAY, PH.D.**, Associate Professor of Psychiatry and Behavior Science, University of Nevada School of Medicine.
and
RALPH G. DePALMA, M.D., Chairman and Professor of Surgery, University of Nevada School of Medicine.
"SEX AND YOUR VASCULAR SYSTEM"

pm - 3:30 pm **NORMAN E. SHUMWAY, M.D., PH. D.**, Chairman, Department of Cardiovascular Surgery, Stanford Medical School.
"HEART TRANSPLANTATION AND HEART/LUNG TRANSPLANTATION"

REGISTRATION

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SCIENTIFIC SESSION
FEES: Check one (includes luncheon)

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Nurses	$ 50_____

n to: Nevada State Medical Assn., 3660 Baker Ln., Reno, NV 89509. Or register by phone, (702) 825-6788, Kathy Nigro. Hotel reservation information will be forwarded upon receipt of your registration form.

96th ANNUAL MEETING
SANTA FE • MAY 5-7, 1982 • HILTON IN

WEDNESDAY, MAY 5 HOUSE OF DELEGATES, FIRST MEETING

2:00 pm **Convenes**—Guest Speaker: William Y. Rial, MD, President-elect, American Medical Association, Swarthmore, Pennsylvania

THURSDAY, MAY 6 SCIENTIFIC SESSION

8:00 am **Registration**

8:30 am **FIRST SESSION**—Presiding: Ashley Pond III, MD, President, New Mexico Medical Society
Risks and Benefits of Radiation

8:35 am **Overall View of Radiation in New Mexico** • Jonathan Mann, MD

9:00 am **Radiation Physics and Biology: What the Practitioner Needs to Know** • Louis Rosen, PhD

9:30 am **Low-Level Radiation: Facts and Facilities** • Edward Webster, PhD

10:15 am **BREAK**—VISIT EXHIBITS

10:45 am **Radiation During Pregnancy and Childhood** • Fred A. Mettler, Jr, MD

11:15 am **The Use of Office Radiology Equipment** • Edward Webster, PhD

12:00 noon **LUNCH BREAK**

2:00 pm **SECOND SESSION**—Presiding: Douglas Layman, MD, President-elect, New Mexico Medical Society

2:05 pm **Health Risks From Nuclear Fuel Cycle Activities in New Mexico** • George L. Voelz, M

2:45 pm **Nuclear Waste Disposal in New Mexico: Medical Implications** • Jonathan Mann, MD

3:30 pm **BREAK**—VISIT EXHIBITS

4:00 pm **Medical Management of Radiation Accidents** • Fred A. Mettler, Jr, MD

4:30 pm **Panel—Perception of Medical Risks and Benefits**

R. C. Derbyshire, MD, Moderator
Douglas Layman, MD
Jonathan Mann, MD
Fred A. Mettler, Jr, MD
Louis Rosen, PhD
George Voelz, MD
Edward Webster, PhD

THURSDAY, MAY 6

6:30 pm **SPECIALTY SOCIETY MEETINGS—HILTON INN**
New Mexico Orthopaedic Association and New Mexico Chapter, Western Orthopaedic Association

Program: "The Cameroons"—John Moore, MD
"A Saudi Arabian Experience"—Charles Eberle, MD

EW MEXICO MEDICAL OCIETY

RIDAY, MAY 7

00 am	**Registration**
30 am	**THIRD SESSION**—Presiding: William Liakos, MD, Vice-President, New Mexico Medical Society
35 am	**What's New and What Will It Cost?** • James Christie, MD
15 am	**Cats and Echoes—When to Order What?** • Jeffrey D. Wicks, MD
00 am	**BREAK**—VISIT EXHIBITS
30 am	**Concurrent Workshops**

Radiology—Trauma
Omar Legant, MD
William McPheron, MD

Radiology—Chest
William Ball, MD
James Stevenson, MD

Radiology—Abdominal
Larry Cohen, MD
Fred Hamilton III, MD

00 Noon **NEMPAC LUNCHEON**
Guest Speaker: Representative Joe Skeen

00 pm **House of Delegates, Second Meeting**

UEST SPEAKERS, SCIENTIFIC SESSIONS

. DERBYSHIRE, MD
etary-Treasurer, New Mexico
e Board of Medical Examiners,
President, New Mexico Medical
ety, Santa Fe, New Mexico

ATHAN MANN, MD
stant Director, Office of Health
notion and Disease Prevention
e Health Services Division, New
ico Department of Health and
ronment, Santa Fe, New Mexico

IS ROSEN, PhD
sion Leader, Meson Physics
sion, Los Alamos National
oratories, Los Alamos,
Mexico

AR LEGANT, MD
te Practice—Radiology,
querque, New Mexico

EDWARD WEBSTER, PhD
Professor of Radiology, Harvard Medical School, Chief, Radiological Sciences Division, Director of Radiation Safety, Massachusetts General Hospital, Boston, Massachusetts

FRED A. METTLER, JR, MD
Cancer Research and Treatment Center, Department of Diagnostic Imaging—President, New Mexico Society of Radiologists, Chapter of American College of Radiology, Albuquerque, New Mexico

GEORGE L. VOELZ, MD
Assistant Health Division Leader for Research and Development, Los Alamos National Laboratories, Los Alamos, New Mexico

JAMES H. CHRISTIE, MD
Faculty, Department of Radiology, University of New Mexico School of Medicine, Albuquerque, New Mexico

JEFFREY D. WICKS, MD
Faculty, Department of Radiology, University of New Mexico School of Medicine, Chief, Diagnostic Ultrasound—Cancer Research and Treatment Center, Albuquerque, New Mexico

WILLIAM McPHERON, MD
Private Practice—Radiology, Hobbs, New Mexico

WILLIAM BALL, MD
Faculty, Department of Radiology, University of New Mexico School of Medicine, Albuquerque, New Mexico

For Further Information or Registration Material

CONTACT: NEW MEXICO MEDICAL SOCIETY, 303 San Mateo, NE, Suite 204
Albuquerque, New Mexico 87108 • (505) 266-7868

in memoriam

California Medical Association

BARNES, ROGER W., Loma Linda. Died in January 1982 in Loma Linda, aged 84. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1922. Licensed in California in 1922. Dr. Barnes was a retired member of the Los Angeles County Medical Association.

BARTLEY, HAROLD, Santa Monica. Died January 11, 1982, in Santa Monica of heart disease, aged 66. Graduate of the University of Louisville School of Medicine, 1949. Licensed in California in 1950. Dr. Bartley was a member of the Los Angeles County Medical Association.

BOYES, FREDERICK F., Berkeley. Died December 23, 1981, aged 65. Graduate of the St. Louis University School of Medicine, St. Louis, 1943. Licensed in California in 1944. Dr. Boyes was a member of the Alameda-Contra Costa Medical Association.

DELPHEY, WILLIAM E., Pasadena. Died December 3, 1981, of cerebrovascular accident, aged 78. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1931. Licensed in California in 1931. Dr. Delphey was a member of the Los Angeles County Medical Association.

DOZIER, WILLIAM E., Carmichael. Died January 1, 1982, in Carmichael, aged 51. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1955. Licensed in California in 1956. Dr. Dozier was a member of the Sacramento-El Dorado Medical Society.

EVANS, FREDERICK L., Chico. Died December 16, 1981, in San Francisco of myocardial infarct, aged 59. Graduate of the Marquette University School of Medicine, Milwaukee, 1945. Licensed in California in 1953. Dr. Evans was a member of the Butte-Glenn Medical Society.

LEE, RUSSEL VAN ARSDALE, Palo Alto. Died January 27, 1982, in Portola Valley, aged 86. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1920. Licensed in California in 1920. Dr. Lee was a member of the Santa Clara County Medical Society.

MACMILLAN, DOUGLAS W., Los Angeles. Died February 2, 1982, in Las Vegas, aged 80. Graduate of McGill University Faculty of Medicine, Montreal, 1922. Licensed in California in 1923. Dr. MacMillan was a member of the Los Angeles County Medical Association.

NEWMAN, BEN A., Beverly Hills. Died in November 1981, aged 75. Graduate of the University of Michigan Medical School, Ann Arbor, 1929. Licensed in California in 1937. Dr. Newman was a member of the Los Angeles County Medical Association.

SAMSON, PAUL C., Oakland. Died February 10, 1982, in Piedmont, aged 78. Graduate of the University of Michigan Medical School, Ann Arbor, 1928. Licensed in California in 1936. Dr. Samson was a retired member of the Alameda-Contra Costa Medical Association.

SMITH, JOSEPH J. H., Colton. Died January 25, 1982, in Los Altos, aged 80. Graduate of Rush Medical College, Chicago, 1929. Licensed in California in 1929. Dr. Smith was a retired member of the San Bernardino County Medical Society.

TRAUNER, LAWRENCE M., San Francisco. Died January 7, 1982, aged 79. Graduate of the University of California Medical School, Berkeley-San Francisco, 1928. Licensed in California in 1928. Dr. Trauner was a retired member of the San Francisco Medical Society.

New Mexico Medical Society

GRIFFIN, JOHN F., Albuquerque. Died February 1, 1982, aged 70. Graduate of Cornell University Medical College, New York, 1936. Licensed in New Mexico in 1948. Dr. Griffin was a member of the Albuquerque & Bernalillo County Medical Society.

Washington State Medical Association

AVERY, WILLIAM E., Tacoma. Died September 17, 1981, of adenocarcinoma of the pancreas, aged 66. Graduate of the Creighton University School of Medicine, Omaha, 1940. Licensed in Washington in 1941. Dr. Avery was a retired member of the Pierce County Medical Society.

BENNETT, JAMES CECIL, Seattle. Died October 29, 1981, aged 76. Graduate of the University of Toronto Faculty of Medicine, 1931. Licensed in Washington in 1939. Dr. Bennett was a retired member of the King County Medical Society.

BLACK, IAN, Mount Vernon, WA. Died November 7, 1981, of myocardial infarct, aged 61. Graduate of the University of Edinburgh Faculty of Medicine, Edinburgh, 1951. Licensed in Washington in 1964. Dr. Black was a member of the Skagit Island County Medical Society.

CALDICOTT, JOHN DARVELL, Olympia. Died October 9, 1981, aged 58. Graduate of the University of Glasgow Medical Faculty, Glasgow, 1952. Licensed in Washington in 1958. Dr. Caldicott was a member of the Thurston Mason Medical Society.

KEGEL, RICHARD F. C., Aberdeen, WA. Died October 31, 1981, aged 77. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1934. Licensed in Washington in 1951. Dr. Kegel was a retired member of the Grays Harbor County Medical Society.

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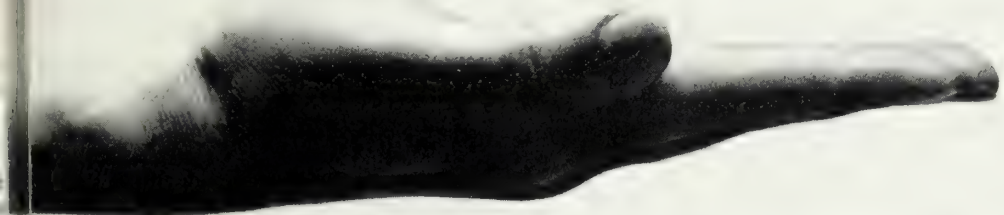

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANALYTICAL HYPNOTHERAPY: Principles and Practice, by Edgar A Barnett, MD. Junica Publishing Co. Ltd., Kingston, Ontario, Canada K7L 4W2, 1981, 497 pages, $35.000.

ANEMIAS, CASE STUDIES: A Compilation of 49 Clinical Studies, by Robert H. Kough, MD; Adel Z. Makary, MD, and Charles T. Thornsvard. 354 pages, Garden City, NY, Medical Examination Publishing Co., Inc., 1981, about $20.

BEDSIDE DIAGNOSTIC EXAMINATION, Fourth Edition, by Elmer L. DeGowin and Richard L. DeGowin, 1,039 pp, with illus, New York, Macmillan Publishing Co., Inc., 1981, $19.95.

CANCER OF THE HEAD AND NECK. Edited by James Y. Suen, MD, and Eugene N. Myers, MD. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1981, 905 pages, $89.00.

CANCER MORTALITY AND MORBIDITY STATISTICS: Japan and the World—Japanese Cancer Association GANN Monograph on Cancer Research No. 26. Edited by Mitsuo Segi, Suketami Tominaga, Kunio Aoki and Isaburo Fujimoto. ISBS, Inc., P.O. Box 1632, Beaverton, OR 97075, 1981, 274 pages, $45.00.

CPR: How To Save a Life Using Cardiopulmonary Resuscitation, by Lindsay R. Curtis, MD; illustrated by Paul Farber. HP Books, P.O. Box 5367, Tucson, AZ 85703, 1981, 64 pages, $3.95, plus $1.00 postage and handling (paperback).

CURRENT MEDICAL DIAGNOSIS & TREATMENT 1982. Edited by Marcus A. Krupp, MD, and Milton J. Chatton, MD; with associate authors. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1982, 1,114 pages, $23.00.

CURRENT PSYCHIATRIC THERAPIES—Volume 20. Edited by Jules H Masserman, MD. Grune & Stratton, Inc., 111 Fifth Avenue, New York, NY 10003, 1981, 416 pages, $54.50.

DIAGNOSIS AND MANAGEMENT OF PERIPHERAL VASCULAR DISEASE. Editor: D. Craig Miller, MD; Associate Editor: Anthony J. Roon, MD; Series Editor: Donald C. Harrison, MD; Foreword by Norman E. Shumway, MD, PhD. Addison-Wesley Publishing Company, Inc., Health Sciences Division, 2727 Sand Hill Road, Menlo Park, CA 94025, 1982, 314 pages, $34.95.

DIVING MEDICINE, by Alex Weisskopf, MD, 36 pages, Rochester, MN, American Academy of Otolaryngology—Head and Neck Surgery, 1981, price not given.

DOUGLAS-STROMME OPERATIVE OBSTETRICS—Fourth Edition, by Edward J. Quilligan, MD, and Frederick Zuspan, MD; contributions by William J. Ledger, MD; Barry S. Schifrin, MD, and Feizal Waffarn, MD Appleton-Century-Crofts, 292 Madison Avenue, New York, NY 10017, 1982 967 pages, $68.50.

DRUGS DURING PREGNANCY: Clinical Perspectives, by Raja W. Abdul Karim, MD; with contributions by Howard J. Osofsky, MD, PhD; Donald R Mattison, MD, and Roger Scott, JD. George F. Stickley Company, 210 West Washington Square, Philadelphia, PA 19106, 1981, 152 pages, $15.00.

EMERGENCY ROOM, by Randall Sword, MD. Charles Scribner's Sons 597 Fifth Ave., New York, NY 10017, 1982, 224 pages, $12.95.

FACELIFTS: Everything You Always Wanted To Know, by Norma Lee Browning. Doubleday & Company, Inc., 245 Park Avenue, New York, NY 10017, 1982, 224 pages, $14.95.

FUNCTIONAL MAPPING OF ORGAN SYSTEMS AND OTHER COMPUTER TOPICS. (11th Annual Symposium on the Sharing of Computer Programs and Technology in Nuclear Medicine.) Edited by Peter D. Esser, 264 pp New York, The Society of Nuclear Medicine, 1981, list price: $28.00 member price: $19.00. Add $2.50 postage and handling per book.

HANDBOOK OF SURGERY—Seventh Edition. Edited by Theodore R Schrock, MD. Jones Medical Publications, 355 Los Cerros Drive, Greenbrae, CA 94904, 1982, 582 pages, $11.95.

HOLISTIC HEALTH IN PERSPECTIVE, by Phyllis H. Mattson, MS. Mayfield Publishing Company, 285 Hamilton Ave., Palo Alto, CA 94301, 1982 200 pages, $6.95 (paperback).

LIFELONG SEXUAL VIGOR, by Marvin B. Brooks and Sally West Brooks 249 pp, Garden City, NY, Doubleday & Company, Inc., 1981, $12.95.

LIVER METASTASIS—Volume Five in the series: METASTASIS. Edited by Leonard Weiss, ScD, MD, PhD, and Harvey A. Gilbert, MD. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston, MA 02111, 1982, 396 pages $55.00.

MANAGING OB/GYN EMERGENCIES. Edited by John T. Queenan, MD Medical Economics Books, Box 157, Florence, KY 41042, 1982, 157 pages $15.95*. *Price is subject to change. Contact publisher for correct price after June 1, 1982.

MEDICAL OBITUARIES: American Physicians' Biographical Notices In Selected Medical Journals Before 1907, by Lisabeth M. Holloway, with the assistance of Ernest N. Feind and George N. Holloway. 513 pages, Garland Publishing, Inc., 136 Madison Ave., New York, NY 10016, 1981, $100.00.

MICROBIOLOGY, edited by Abraham I. Braude, MD, PhD; Associate Editors: Charles E. Davis, MD, and Joshua Fierer, MD. W. B. Saunders Company, West Washington Square, Philadelphia, PA 19105, 1982, 845 pages, $19.95 (US); $23.95 (Canada).

OFFICE GYNECOLOGY, Second Edition. Edited by Robert H. Glass, MD. 360 pp, illustrated, Baltimore, Williams & Wilkins, 1981, $32.00.

PATIENTS AND HEALERS IN THE CONTEXT OF CULTURE—An Exploration of the Borderland Between Anthropology, Medicine, and Psychiatry, by Arthur Kleinman. University of California Press, 2223 Fulton Street, Berkeley, CA 94720, or 50 East 42nd St., Rm 513, New York, NY 10017, 1980, 427 pages, $9.95 (paperback); $29.50 (cloth).

RENAL MEDICINE—Second Edition, by Roger Gabriel, BA, MSc, MB, FRCP. London, Balliere Tindall, 1981. Macmillan Publishing Co., Inc., 866 Third Ave., New York, NY 10022, 266 pages, $16.95.

REVIEW OF ALLIED HEALTH EDUCATION: 4. General Editor: Joseph Hamburg, MD; Associate Editors: Darrel J. Mase, PhD, and J. Warren Perry, PhD. The University Press of Kentucky, Lexington, KY 40506, 1981, 148 pages, $13.00.

ROGUES, REBELS, AND GENIUSES—The Story of Canadian Medicine, by Donald Jack. Doubleday & Company, Inc., 245 Park Avenue, New York, NY 10017, 1981, 662 pages, $24.95.

SAFER CANCER CHEMOTHERAPY. Edited by L. A. Price, MD, MRCP; Bridget T. Hill, PhD, FRIC, FIBiol, and M. W. Ghilchik, BSc, MS, FRCS. Balliere Tindall, London, 1981. Macmillan Publishing Co., Inc., 866 Third Avenue, New York, NY 10022, 124 pages, $25.00.

SPORTS MEDICINE: Fitness, Training, Injury. Edited by Otto Appenzeller and Ruth Atkinson. 395 pp, with 119 illus, Baltimore, Urban & Schwarzenberg, Inc., 1981, $39.50.

SOCIAL WORK AND DIALYSIS—The Medical and Psychosocial Aspects of Kidney Disease, by Carrie L. Fortner-Frazier. University of California Press, 2223 Fulton St., Berkeley, CA 94720, or 50 East 42nd St., Rm 513, New York, NY 10017, 1981, 228 pages, $16.50.

SOMETHING HIDDEN—A Biography of Wilder Penfield, by Jefferson Lewis. Doubleday & Company, Inc., 245 Park Ave., New York, NY 10017, 1981, 311 pages, $17.95.

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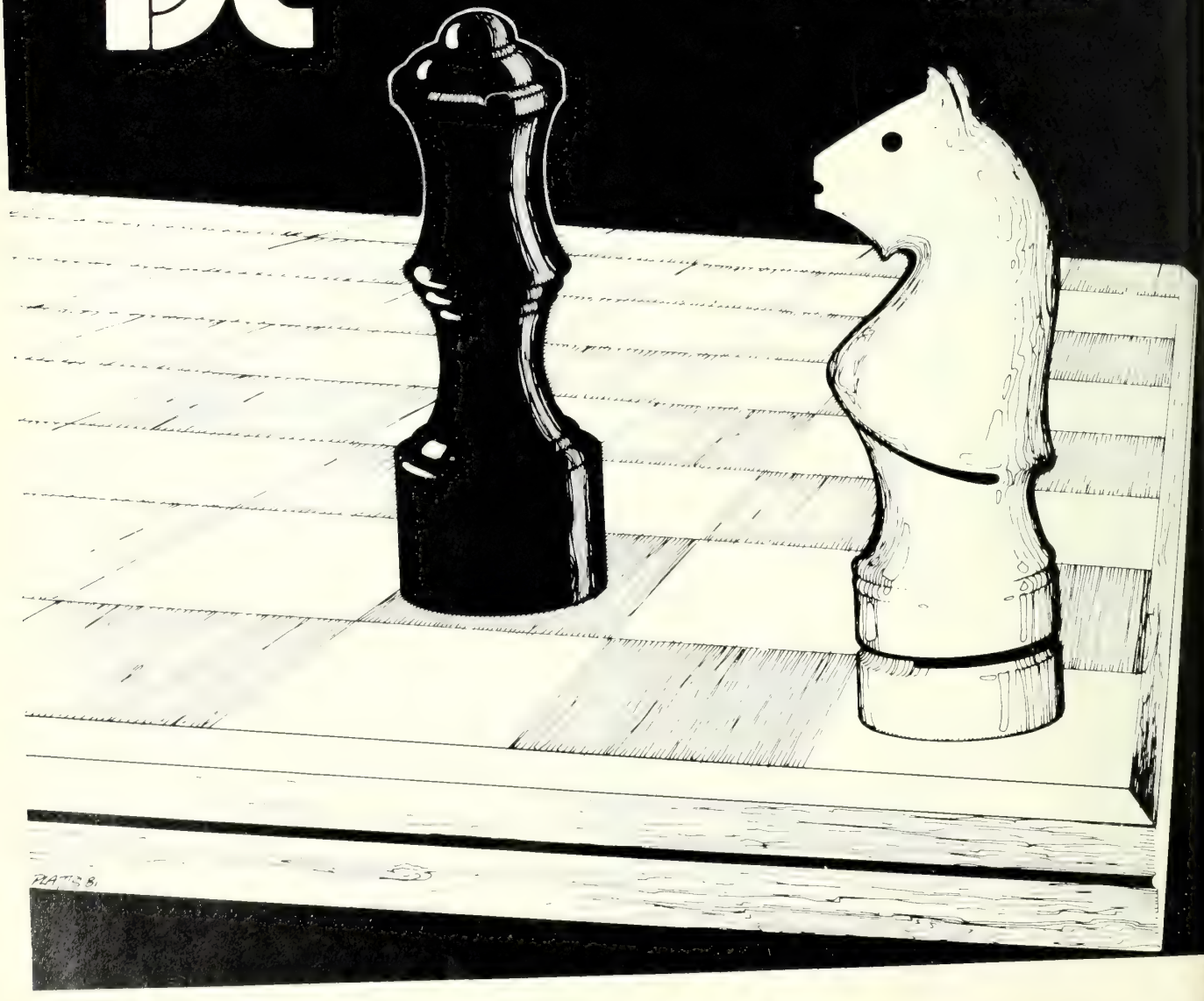

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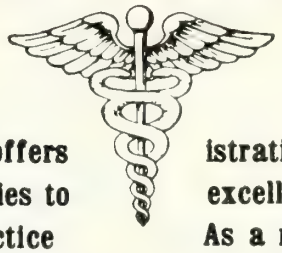

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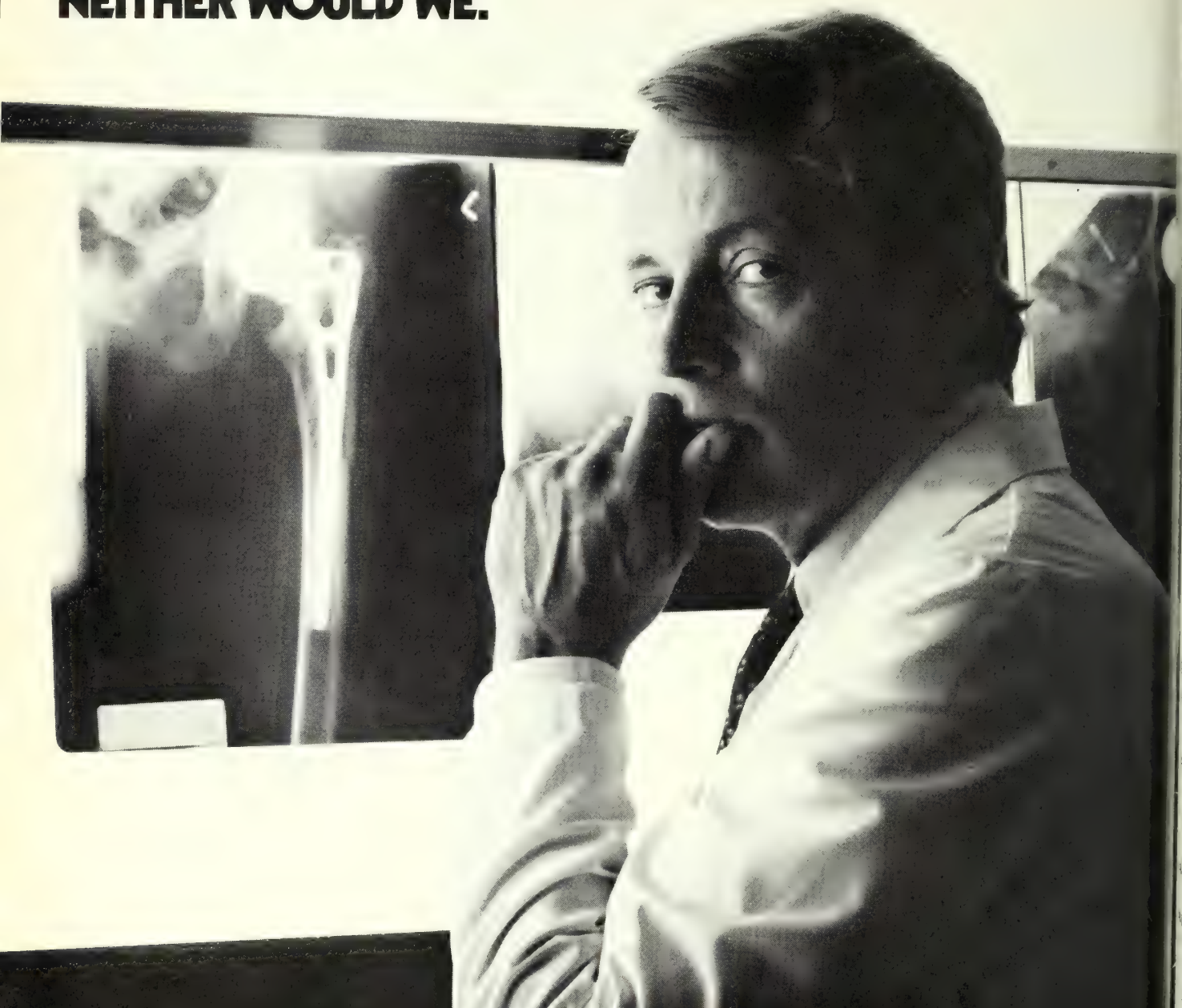

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(Continued from Page 39)

nual Meeting. MGM Grand, Reno. Thursday-Saturday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103.

October 24-27—**American Association for Clinical Immunology and Allergy.** Town and Country, San Diego. Sunday-Wednesday. Contact: Howard Silber, Exec. Dir., P.O. Box 912-DTS, Omaha, NE 68101. (402) 551-0801.

OBSTETRICS AND GYNECOLOGY

April 19-21—**4th Annual Orange County OB/GYN Congress.** Orange County Ob-Gyn Society and UCI at Newporter Inn, Newport Beach. Monday-Wednesday. 15 hrs. $250. Contact: Secretary, P.O. Box 1297, Orange 92668. (714) 644-1700.

May 10-12—**Recent Advances in OB/GYN.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 20 hrs. $300.

May 19-21—**Perinatal Medicine: Issues and Impact.** Mount Zion Hospital and Medical Center at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday. Contact: Office of Cont. Ed., Mount Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

May 22—**Breast-Feeding in the 80s: Recent Developments and Current Views.** See Pediatrics, May 22.

June 2-5—**Controversies in Obstetrics and Gynecology.** Memorial Hospital Medical Center-UCI Center for Health Education at Silverado Country Club, Napa. Wednesday-Saturday. 20 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 10-15—**Reproductive Health Care—Changing Concepts in Fertility Regulation.** Wayne State University at Marriott, Maui. Sunday-Friday. Contact: E. S. E. Hafez, Dept. of Obstetrics/Gynecology, Wayne State Univ., Sch. of Med., Med. Research Bldg., Rm 416, 5500 E. Canfield, Detroit 28201. (313) 577-1011.

PEDIATRICS

April 16-17—**Pediatrics: Renal Disease in Children and Adolescents.** UCD at Holiday Inn Holidome, Sacramento. Friday-Saturday. 11 hrs.

April 16-17—**New Directions in Care of the Handicapped Child.** American Academy of Pediatrics and Desert Hospital at Desert Hospital, Palm Springs. Friday-Saturday. 16 hrs. Contact: John Powers, AAP, P.O. Box 1034, Chicago 60602. (800) 323-0797.

April 22-24—**Advances in Pediatrics.** UCSF. Thursday-Saturday. 18 hrs. $250.

April 28-30—**7th Annual Symposium: Care of the Sick Newborn.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 19 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 1—**Pediatric Ophthalmology for the Primary Care Practitioner.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 6 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 3-7—**12th Annual Review of Pediatrics.** USC. Monday-Friday. 32 hrs. $350.

May 19—**Los Angeles Pediatric Society—Annual Spring Meeting.** Hilton, Los Angeles. Wednesday. 2 hrs. $20. Contact: Eve Black, Exec. Sec., P.O Box 2022, Inglewood 90305. (213) 757-1198.

May 22—**Breast-Feeding in the 80s: Recent Developments and Current Views.** UCLA. Saturday. 7 hrs. $65.

May 29-31—**Challenges in Pediatrics.** Northern California Chapter, American Academy of Pediatrics, at Monterey. Saturday-Monday. Contact: David A. Zlotnick, MD, 3200 Middlefield Rd., Palo Alto 94306.

July 11-12—**First Annual Disneyland Pediatric Seminar.** American Academy of Pediatrics, Calif. Chap. 2, at Disneyland Hotel, Anaheim. Sunday-Monday. 12 hrs. Contact: AAP, Calif. Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

September 29-30—**39th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Hilton, Los Angeles. Wednesday-Thursday. 11 hrs. $145, members; $175, nonmembers. Contact: Eve Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

PSYCHIATRY

April 23-24—**Psychotherapy and Law Enforcement: Issues and Techniques.** UCSF at Hyatt Regency, San Francisco. Friday-Saturday. Contact: Aveleen Blumenstock, Asst. Dir. of Cont. Ed., Dept. of Psychiatry, UCSF, Langley Porter Institute, Box 2D, 401 Parnassus Ave., San Francisco 94143. (415) 681-8080, ext. 554.

May 15—**Memory Loss—An Increasing Clinical Problem.** UCLA. Saturday. 6 hrs. $85.

June 3-5—**Depression.** UCD at Del Monte Hyatt, Monterey. Thursday-Saturday.

June 21-25—**Comparative Psychotherapies.** USC at Vacation Village, San Diego. Monday-Friday. 21 hrs. $295.

October 9-10—**Sexual Deviation: Contemporary Psychoanalytic Views.** So. Calif. Psychoanalytic Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Contact: Mrs. Carol Ziff, Exec. Sec., SCPS, 9024 Olympic Blvd., Beverly Hills 90211. (213) 936-2877.

RADIOLOGY AND PATHOLOGY

April 30-May 1—**CT of the Lumbar Spine.** UCSF at Fairmont Hotel, San Francisco. Friday-Saturday. 11 hrs. $250.

May 6-8—**Ultrasonic Update.** UCI at Anaheim. Thursday-Saturday. 18 hrs. Contact: Kim Stroich, 14761 Franklin Ave., Suite A, Tustin 92680. (714) 832-2650.

May 7-8—**Common Nervous System Pathology Diagnosis and Treatment.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 14 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 20-25—**Pathology of the Lung.** UCSD at La Jolla Village Inn, La Jolla. Sunday-Friday. 50 hrs.

July 24-30—**Laboratory Medicine.** USC at Maui Marriott Resort, Maui. One week. 27 hrs. $435.

July 24-August 1—**Diagnostic Radiology: An In-Depth Seminar Approach to Diagnostic Imaging.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. 9 days. 24 hrs. $345.

August 7-14—**Radiology.** USC at Mauna Kea Beach Hotel, Kamuela. One week.

August 30-September 1—**Napa Valley Radiology Conference.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at Napa Valley. Monday-Wednesday. 18 hrs. $275. Contact: Michael H. Reid, PhD, MD, Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

September 25—**Clinical Ultrasound in Obstetrics and the Neonatal Period.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at Sacramento. Saturday. 6 hrs. $75. Contact: J. P. McGahan, MD, Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

October 7-10—**Society of Nuclear Medicine—7th Annual Western Regional Meeting.** Town and Country Hotel, San Diego. Thursday-Sunday. Contact: Jean Parker, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact:

Radiology Postgraduate Ed. Section. UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

April 15-17—**Postgraduate Course in General Surgery.** UCSF. Thursday-Saturday.

April 17-24—**Frontiers in Functional Neurosurgery.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 21-23—**American Intra-Ocular Implant Society.** Century Plaza, Los Angeles. Wednesday-Friday. Contact: AIOIS, P.O. Box 3140, Santa Monica 90403. (213) 829-7317.

April 23-24—**Vitrectomy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

April 24-May 1—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $325.

April 25-29—**American Association of Neurological Surgeons.** Honolulu. Sunday-Thursday. 40 hrs. Contact: Selene Patterson, AANS, 625 N. Michigan Ave., Suite 1519, Chicago 60611. (312) 944-4205.

April 26-29—**Southwestern Surgical Congress.** Hotel del Coronado, Coronado. Monday-Thursday. Contact: J. A. Barney, MD, 1211 N. Shartel St., 708 Physicians and Surgeons Bldg., Oklahoma City 73103.

April 30-May 1—**CT of the Lumbar Spine.** See Radiology and Pathology.

May 2-6—**American Society of Colon and Rectal Surgeons—Annual Convention.** San Francisco. Sunday-Thursday. 20 hrs. $125, members: $135, nonmembers. Contact: Harriette Gibson, Admin. Sec., ASCRS, 615 Griswold, Suite 516, Detroit 48226. (313) 961-7880.

May 11-14—**3rd Annual Verne T. Inman/17th Annual LeRoy C. Abbott Lectureship.** UCSF. Tuesday-Friday. 14 hrs. Contact: Eileen Gaines, Alumni Sec., UCSF Dept. of Orthopedic Surgery, U471, San Francisco 94143. (415) 666-1166.

May 12—**Surgical Subspecialties.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Secretary, Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

May 14-15—**Diagnostic Ocular and Orbital Ultrasound Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $125. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

May 21-22—**Modern Concepts in Trauma Care.** Orange County Trauma Society and Mission Community Hospital at Disneyland Hotel, Anaheim. Friday-Saturday. 14 hrs. $195. John G. West, MD, Orange Co. Trauma Soc., 321 N. Rampart, Suite 120, Orange 92668. (714) 937-5030.

June 2-4—**OTO 83.** Project HEAR at Hyatt Regency, San Francisco. Wednesday-Friday. 24 hrs. Contact: Project HEAR, 1801 Page Mill Rd., Palo Alto 94304. (415) 494-2000.

June 3-4—**12th Annual Neurosurgery Postgraduate Course.** UCSF at Hilton, San Francisco. Thursday-Friday. 16 hrs. $250.

June 4-7—**Intensive Course in Refractive Keratoplasty: Barraquer Technique.** Jules Stein Eye Institute, Los Angeles. Friday-Monday. 32 hrs. $1,750. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

June 19-26—**Medical and Surgical Management of Ocular Inflammation.** USC at Mauna Kea Beach Hotel, Kamuela. One week. 26½ hrs. $435.

August 12-14—**Selection and Technique for Use of Muscle and Musculocutaneous Flaps in Reconstructive Surgery.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 20 hrs. $420.

August 14-25—**Update: Surgery 1982.** USC at Sheraton Waikiki, Honolulu, and Maui Marriott Resort, Maui. 12 days. 35 hrs. $425.

September 1-3—**International Cochlear Symposium.** UCSF at Holiday Inn Union Square, San Francisco. Wednesday-Friday.

September 12-25—**Temporal Bone Surgical Dissection Course.** House Ear Institute, Los Angeles. Two weeks. 100 hrs. $1,500. Contact: Antonio De La Cruz, MD, House Ear Inst., 256 S. Lake St., Los Angeles 90057.

September 29-October 1—**New Concepts in Maxillofacial Surgery.** STAN and Swiss Assn. for the Study of Internal Fixation at Stanford. Wednesday-Friday. 17 hrs. Contact: ASIF Course Secretariat, P.O. Box 514, Wayne, PA 19087. (215) 293-0654.

October 10-15—**American Society of Plastic and Reconstructive Surgeons.** Sheraton Waikiki, Honolulu. Sunday-Friday. Contact: ASPRS, c/o Plastic Surgery News, 3580 Hythe Ct., Columbus, OH 43220.

October 15-16—**Advanced Seminar in Urologic Surgery.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

October 30—**Diagnosis and Treatment of Nasal Disorders.** UCSD. Saturday.

October 31-November 5—**American Academy of Ophthalmology.** San Francisco. Sunday-Friday. Contact: AAO, 2340 Clay St., San Francisco 94115.

OF INTEREST TO ALL PHYSICIANS

April 17—**Nutritional Concerns in the Hospitalized Patient.** Fresno Community Hospital and Medical Center at Hilton, Fresno. Saturday. 8 hrs. $50. Contact: Education and Training Dept., Fresno Community Hosp. and Med Ctr., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

April 22-24—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 22-25—**Wound Management.** UCSD at Hilton, San Diego. Thursday-Sunday. 20 hrs.

April 22-25—**Mountain Medicine.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Friday-Sunday. 19 hrs.

April 23-25—**Physicians—Stress and Coping.** CMA at The Inn, Rancho Sante Fe. Friday-Sunday. 14 hrs. $190 per couple or $120 per person. Contact: Sandy Willett, CMA.

April 30-May 1—**Acute Medical Care—1982—8th Annual Spring Meeting.** Providence Hospital at Marriott Inn, Berkeley. Friday-Saturday. $25. Contact: Medical Staff Office, Providence Hosp., Box 23020, Oakland 94623. (415) 874-8003.

April 30-May 2—**Physicians—Stress and Coping.** CMA at El Encanto, Santa Barbara. Friday-Sunday. 14 hrs. $190 per couple or $120 per person. Contact: Sandy Willett, CMA.

May 1-8—**Diagnostic and Therapeutic Skills.** USC at Hawaii. One week. 29 hrs. $425.

May 2-5—**Medical Evaluation of the Preoperative Patient.** UCD at Del Monte Hyatt, Monterey. Sunday-Wednesday. 17 hrs. $245.

May 2-5—**American Medical Informatics Association Congress 82—First Annual Joint Conference.** AMIA, Soc. for Advanced Medical Systems, Soc. for Computer Medicine, Internat'l Health Evaluation Assn., Salutis Unitas, Univ. of Missouri-Columbia Health Care Technology Ctr., IL Conf on Medical Information Systems, at Hyatt on Union Square San Francisco. Sunday-Wednesday. Contact: M. F. Collen MD, 3451 Piedmont Ave., Oakland 94611.

May 3-7—**Symposium on Non-Emergent Outpatient Care** UCSD at Hilton, San Diego. Monday-Friday. 27 hrs. $325

May 3-9—**Basic Diving Medicine.** UCSF at Fresno. One week Contact: Vincent S. O'Hara, MD, VA Medical Center, 261 E. Clinton, Fresno 93703. (209) 225-6100, ext. 345.

May 6-9—**Association of Clinical Scientists.** Miramar Sheraton, Los Angeles. Thursday-Sunday. Contact: F. W. Sunderman, Jr., MD, Dept. of Laboratory Medicine, Univ. of Connecticut Sch. of Med., 263 Farmington Ave., Farmington, CT 06032.

May 9-13—**Association for the Advancement of Medical Instrumentation.** Hyatt Regency, San Francisco. Monday-Thursday. Contact: M. J. Miller, Exec. Dir., Assn. for the Advancement of Medical Instrumentation, 1901 N. Ft. Myer Dr., Suite 602, Arlington, VA 22209.

May 9-14—**Fingers-to-Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Friday. 40 hrs. $375.

May 12—**Common Fractures.** LLU. Wednesday. 4 hrs. $30.

May 14-16—**Physicians—Stress and Coping.** CMA at Stanford Sierra Lodge, Fallen Leaf Lake. Friday-Sunday. 14 hrs. $190 per couple or $120 per person. Contact: Sandy Willett, CMA.

May 15-16—**Chronic Low Back Pain—The Causes and Successful Management.** UCLA. Saturday-Sunday. 10 hrs. $135.

May 15-16—**Hypnosis for Primary Care Physicians (Intermediate Level Course).** Alta Bates Hospital, Berkeley. Saturday-Sunday. 14 hrs. $170. Contact: Med. Ed. Dept., Alta Bates Hosp., 3001 Colby St., Berkeley 94705. (415) 845-7110, ext. 2055.

May 22-23—**Conference on Health Problems Related to the Chinese in America.** Chinese Hospital and UCSF at Holiday Inn/Financial District, San Francisco. Saturday-Sunday. 12 hrs. $85. Contact: Elizabeth S. Weston, Chinese Hosp., 845 Jackson St., San Francisco 94133. (415) 982-2400, ext. 215.

May 28-30—**Physicians—Stress and Coping.** CMA at Asilomar, Pacific Grove. Friday-Sunday. 14 hrs. Contact: Sandy Willett, CMA.

May 31—June 4—**9th Annual Joint UCLA-Santa Monica Hospital Medical Center Family Practice Refresher Course.** Miramar-Sheraton, Santa Monica. Monday-Friday. 35 hrs. Contact: UCLA.

June 5—**The Medical Consequences of Nuclear War: Rx for Prevention.** UCSD at Civic Center, San Diego. Saturday. 6 hrs. $45.

June 9-11—**7th Annual Conference: Clinical Application of Hyperbaric Oxygen.** Memorial Hospital Medical Center at Disneyland Hotel, Anaheim. Wednesday-Friday. 24 hrs. Contact: Baromedical Dept., Memorial Hosp. Med Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3613.

June 14-19—**UCI Family Practice Refresher Course.** Marriott, Newport Beach. Sunday-Friday. 50-56 hrs.

July 6-8—**Family Practice Board Review Course.** UCSF. Tuesday-Thursday.

July 9-11—**Sensory Systems' Influence on Movement and Tone —10th Annual Sensorimotor Integration Symposium.** UCSD at Holiday Inn at the Embarcadero, San Diego. Friday-Sunday.

August 12-13—**National Institute for Care of the Elderly.** Univ. of Nevada-Reno School of Medicine at MGM Grand, Reno. Thursday-Friday. 12 hrs. Contact: Leanne Stone, Cont. Ed., Univ. of Nevada-Reno, Reno 89557. (702) 784-4046.

August 13-14—**6th Annual Sports Medicine Conference.** Univ. of Nevada-Reno School of Medicine at MGM Grand, Reno. Friday-Saturday. 12 hrs. Contact: Leanne Stone, Cont. Ed., Univ. of Nevada-Reno, Reno 89557. (702) 784-4046.

August 14-25—**25th Annual Postgraduate Refresher Course.** USC at Sheraton Waikiki, Honolulu, and Maui Marriott Resort, Maui. 12 days. 37 hrs. $425.

August 16-20—**Advanced Diving Medicine.** UCSF at San Diego. Monday-Friday.

August 23-September 3—**Intensive Residency in Occupational Medicine, Session. I.** UCSF at Golden Gateway Holiday Inn, San Francisco. 12 days. 80 hrs. $1,000.

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August 27-29—**Physicians—Stress and Coping.** CMA at La Playa Hotel, Carmel. Thursday-Sunday. 14 hrs. $190 per couple or $120 per person. Contact: Sandy Willett, CMA.

September 10-12—**Physicians—Stress and Coping.** CMA at Sea Lodge, La Jolla. Thursday-Sunday. 14 hrs. $190 per couple or $120 per person. Contact: Sandy Willett, CMA.

September 16-18—**Postgraduate Institute on Geriatrics.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 4-7—**American Academy of Family Physicians—1982 Scientific Assembly.** Moscone Center, San Francisco. Monday-Thursday. 30+ hrs. $50, members; $75, nonmembers. Contact: Edward E. Daleske, Committee on Scientific Prog., AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

October 8-10—**Physicians—Stress and Coping.** CMA at Half Moon Bay Lodge, Half Moon Bay. Thursday-Sunday. 14 hrs. $190 per couple or $120 per person. Contact: Sandy Willett, CMA.

October 10-15—**American Physiological Society—33rd Annual Fall Meeting.** Town and Country, San Diego. Sunday-Friday. Contact: Geri Goodenough, Scientific Meetings, APS, 9650 Rockville Pike, Bethesda, MD 20814. (301) 530-7010.

October 11-14—**Hawaii Medical Association—126th Annual Scientific Meeting.** Hilton Hawaiian Village, Honolulu. Monday-Thursday. Contact: Irene Wong, HMA, 320 Ward Ave., Honolulu 96814. (808) 536-7702.

October 28-30—**West Coast Counties Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

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Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA

See Washington Listings: May 3, 4, 6-7, 26; June 7, 8, 17-18.

IDAHO

See Washington Listings: April 19, May 29 and June 14.

MONTANA

October 30-November 2—**Montana Medical Association Annual Meeting.** Great Falls. Friday-Tuesday. Sheraton. For information contact: Montana Medical Association, 2011 Eleventh Avenue, Suite 12, Helena, MT 59601. (406) 443-4000.

See Washington Listings: April 15-17, 21, 22, 23; May 26, 27, 28; June 7 and 8.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 23-24—**Geriatrics Medicine Update—1982.** Albuquerque. Friday-Saturday. AMFAC Hotel. 10 credit hours, also AAFP Prescribed. Contact: UNM School of Medicine, Office of CME, Albuquerque, NM 87131. (505) 277-3942.

May 5-7—**New Mexico Medical Society Annual Meeting—Risks and Benefits of Radiation.** Santa Fe. Wednesday-Friday. Hilton Inn. 11 credit hours, also AAFP. Contact: NMMS, 303 San Mateo NE, #204, Albuquerque, NM 87108. (505) 266-7868.

May 6-8—**Arrythmia Diagnosis and Management for the Non-Cardiologist.** Santa Fe. Thursday-Saturday. Inn at Loretto. 18 credit hours, also AAFP Prescribed. Fee $150. Contact: Barry W. Ramo, MD, 201 Cedar SE, #604, Albuquerque, NM 87106.

May 8—**New Mexico Pathological Society and New Mexico OB/GYN Society Joint Meeting: Update in Gestational Trophoblastic Neoplasms.** Santa Fe. Saturday. Hilton Inn. 4 credit hours. Contact: Robert Hilgers, MD, UNM School of Medicine, 900 Camino de Salud NE, Albuquerque, NM 87131. (505) 277-2858.

May 14-15—**15th Annual OB/GYN Update.** Albuquerque. Friday-Saturday. AMFAC Hotel. 10 credit hours, also AAFP Prescribed. Contact: UNM School of Medicine, Office of CME, Albuquerque, NM 87131. (505) 277-3942.

June 4-5—**Recent Advances in the Diagnosis and Treatment of Coronary Artery Disease.** Albuquerque. Friday-Saturday. Veterans Administration Medical Center. 10 credit hours, also AAFP Prescribed. Contact: American Heart Association, 2403 San Mateo Blvd., Albuquerque, NM 87108. (505) 884-3717.

June 17-19—**Radiology for Primary Care Physicians 1982—An Update.** Santa Fe. Thursday-Saturday. Symposia de Santa Fe. 15 credit hours, also AAFP Prescribed. Contact: Marcus J. Smith, MD, PO Box 5175, Santa Fe, NM 87501. (505) 982-5218.

July 8-10—**25th Annual Meeting, New Mexico Ophthalmological Society.** Santa Fe. Thursday-Saturday. Hilton Inn. 8 credit hours. Contact: Walter J. Levy, MD, 465 St. Michael's Dr., Santa Fe, NM 87501. (505) 982-1911.

July 19-22—**25th Annual Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 credit hours. Also AAFP Prescribed. Contact: Convention Director, NM Academy of Family Physicians, PO Box 456, Sunland Park, NM 88063. (505) 266-7868 or (915) 533-3449.

July 23-25—**11th Annual Santa Fe Cardiology Symposium.** Santa Fe. Friday-Sunday. Inn at Loretto. 14 credit hours, also AAFP Prescribed. Contact: Meeting Director, Southwest Cardiology Associates, 8100 Constitution NE, Albuquerque, NM 87110. (505) 292-1114.

October 7-9—**The Clinical Spectrum of Adult Heart Disease.** Albuquerque. Thursday-Saturday. University of New Mexico School of Medicine Auditorium. Hour for hour credit, also AAFP Prescribed. Contact: Jonathan Abrams, MD, UNM School of Medicine, Dept. of Cardiology, Albuquerque, NM 87131. (505) 277-4253.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Everly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sci-

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ences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

EMERGENCY MEDICINE

September 17-18—**Poisoning and Toxicological Emergencies.** Portland. Friday-Saturday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

OBSTETRICS AND GYNECOLOGY

October 21-23—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

SURGERY

June 4-5—**Orthopedics for the Primary Care Physician.** Portland. Friday-Saturday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

December 3—**Soft Tissue Surgery Techniques.** Portland. Friday. Oregon Health Sciences University Campus. For information contact: OHSU-CME.

INTEREST TO ALL PHYSICIANS

April 14-16—**Sommer Lectures—School of Medicine Alumni Meetings.** Portland. Wednesday-Friday. Oregon Health Sciences University Campus. For information contact: OHSU-CME.

April 23-24—**Update in Rheumatology.** Portland. Friday-Saturday. Marriott Hotel. For information contact: OHSU-CME.

May 14-15—**Medical Genetics in Clinical Practice.** Portland. Friday-Saturday. Thunderbird Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

June 24-25—**Urology for the Non-Urologist.** Portland. Thursday-Friday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

September 10-11—**Ashland Conference: Infectious Diseases.** Ashland. Friday-Saturday. Ashland Hills Inn. For informamation contact: OHSU-CME.

September 17-18—**Poisoning and Toxicological Emergencies.** Portland. Friday-Saturday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

October 29-31—**Salishan Conference: Cardiology.** Gleneden Beach. Friday-Saturday. Salishan Lodge. For information contact: OHSU-CME.

November 18-19—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

MKSAP V REVIEW

(Sponsors: Utah Region, American College of Physicians/Utah Society of International Medicine/University of Utah)
University Medical Center, Salt Lake City
October 1981-June 1982 (Ongoing)—Thursdays. 2 hrs. Fee for Optional Materials: $160 (ACP non-members); $60 (ACP members). Contact: John Holbrook, MD (801) 581-7818.

* * * *

April 15-17—**First Annual Clinical Ophthalmology Meeting at Snowbird** (Sponsor: University of Utah). Snowbird. Tuesday-Thursday. 9 hrs. Fee: $50. Contact: Rebecca Olsen (801) 581-6384.

May 14-15—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

June 11-12—**Medical Aspects of Laser Surgery** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Little America. Credit and fee to be announced. Contact: Johr Dixon, MD (801) 581-8201.

Note: Dates, times, places and programs are subject to change or occasion. Please check with the sponsoring organization or the Academy for details.

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

April 14—**Alcoholism.** Tacoma. Wednesday. Puget Sound Hospital. Contact: CME Pierce County.

April 15-17—**Eleventh Annual Refresher Course in Diagnostic Radiology and Spinal CT Symposium.** Spokane. Thursday-Saturday. Sacred Heart Medical Center. Contact: Marvin J. Gottschall, MD, Director of Radiology, Sacred Heart Medical Center, TAF-C9, Spokane, WA 99220. (509) 455-3131.

April 15-17—**(MONTANA) Cytology Continuing Education Workshop.** Billings. Thursday-Saturday. Contact: CME Harborview.

April 17-24—**(HAWAII) Frontiers in Functional Neurosurgery.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 19—**(IDAHO) Early Cervical Cancer.** Boise. Monday. Contact: U/W.

April 20—**Detection/Rx Early Cervical Cancer.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

April 21—**Interstitial Lung Disease.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

April 21—**(MONTANA) What's New in Diabetes.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

April 22—**(MONTANA) What's New in Diabetes.** Billings. Thursday. Marillac Hall. Contact: U/W.

April 22-23—**Vascular Disease 1982: A Comprehensive Review for Primary Physicians.** Seattle. Thursday-Friday. South Campus Center. Contact: U/W.

April 23—**Surgical Club Annual Meeting.** Tacoma. Friday. Tacoma General Hospital. Contact: CME Pierce County.

April 23—**(MONTANA) What's New in Diabetes.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

April 26—**Urinary Infections New Developments in Nosocomial Infections.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

April 28—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

April 28-30—**Children's Orthopedic Hospital and Medical Center 75th Anniversary Pediatric Symposium.** Seattle. Wednesday-Friday. Children's Orthopedic Hospital and Medical Center. Contact: Donna Neumann, Medical Administration Office, Children's Orthopedic Hospital and Medical Center, P.O. Box 65371, Seattle, WA 98105. (206) 634-5377.

April 29-May 1—**Trauma.** Seattle. Thursday-Saturday. University of Washington South Campus Center. Contact: U/W.

May 3—**Site Visit.** Omak. Monday. Contact: U/W.

May 3—**(ALASKA) Site Visit.** Ketchikan. Monday. Contact: U/W.

May 4—**(ALASKA) Site Visit.** Anchorage. Tuesday. Contact: U/W.

May 4—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

May 6-7—**(ALASKA) Cross Cultural Child Psychiatry.** Anchorage. Thursday-Friday. Contact: U/W.

May 7—**The Foot.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

May 13-15—**Third Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 14—**Medical Alumni.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

May 14-15—**Therapeutics in Common Medical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 19—**Breast Cancer & Acute Leukemia.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

May 20—**Estrogen Controversy.** Tacoma. Thursday. Contact: CME Pierce County.

May 20-22—**3rd Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 24—**Fever Unknown Origin/Dx Elderly Dementia.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

May 26—**(ALASKA) Vaginitis.** Anchorage. Wednesday. Contact: U/W.

May 26—**(MONTANA) Health Problems of Physicians.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

May 26—**(MONTANA) Site Visit.** Kalispell. Wednesday. Contact: U/W.

May 27—**(MONTANA) Health Problems of Physicians.** Billings. Thursday. Marillac Hall. Contact: U/W.

May 27—**(MONTANA) Site Visit.** Whitefish. Thursday. Contact: U/W.

May 27-28—**Current Concepts in Management of Joint Disease.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

May 28—**(MONTANA) Health Problems of Physicians.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

May 28-29—**Advanced Cardiac Life Support.** Seattle. Thursday. Contact: U/W.

May 29—**(IDAHO) Site Visit.** Pocatello. Saturday. Contact: U/W.

June 3-5—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

June 7—**(MONTANA) Site Visit.** Kalispell. Monday. Contact: U/W.

June 7—**(ALASKA) Site Visit.** Ketchikan. Monday. Contact: U/W.

June 8—**(ALASKA) Site Visit.** Anchorage. Tuesday. Contact: U/W.

June 8—**(MONTANA) Site Visit.** Whitefish. Tuesday. Contact: U/W.

June 10-12—**Common Minor Surgeries.** Seattle. Thursday-Saturday. Park Hilton. Contact: U/W.

June 14—**(IDAHO) Vaginitis.** Boise. Monday. Contact: U/W.

June 14—**Site Visit.** Omak. Monday. Contact: U/W.

June 15—**Vaginitis.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

June 15—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

June 16—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

June 17-18—**(ALASKA) Behavior Medicine for GP's.** Anchorage. Thursday-Friday. Contact: U/W.

June 19-23—**(BRITISH COLUMBIA, CANADA) Canadian Congress of Laboratory Medicine & Pacific Northwest Society of Pathologists Meeting.** Vancouver, BC. Saturday-Wednesday. Hotel Vancouver. Contact: G. R. Gray, MD, 201-660 West Seventh Avenue, Vancouver, BC V5Z IB5.

June 21-25—**Internal Medicine Review.** Seattle. Monday-Friday. Park Hilton. Contact: U/W.

June 23-27—**(OREGON) Modern Medical Practice.** Ashland. Wednesday-Sunday. Ashland Inn. Contact: U/W.

June 24-25—**EKG Interpretation and Arrythmias.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: June 6-8, 1982, Chena Hot Springs.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. House of Delegates' Annual Meeting: May 28-29, 1982, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 11-16, 1983, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 21-24, 1982, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 11-14, 1982, Hilton Hawaiian Village, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 28-31, 1982, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 30-November 2, 1982, Sheraton, Great Falls.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 14-16, 1982, MGM Grand Hotel, Reno.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. Annual Meeting: May 5-7, 1982, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: November 3-5, 1982, Thunderbird, Jantzen Beach.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: September 14-17, 1982, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 7-10, 1982, Towne Motel, Yakima.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 30-July 3, 1982, Jackson Lake Lodge, Moran.

June 24-26—**Scientific Aspects of Dance.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact: U/W.

June 28—**Recent Advances in Hematology.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

July 15-16—**Surviving the Elements.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

July 23-25—**Washington State Society of Anesthesiologists: Seafair IV Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center. Contact: VMMC.

July 30-31—**Infertility.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

August 19-21—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

September 8-15—**13th International Cancer Congress.** Seattle. Wednesday-Wednesday. Seattle Center. Contact: Congress Operations Office, 13th International Cancer Congress, Fourth and Blanchard Building, Suite 1800, Seattle, WA 98121. (206) 621-9440.

September 16-18—**(WYOMING) Cytology Continuing Education Workshop.** Jackson. Thursday-Saturday. Contact: CME Harborview.

September 23-25—**Cytology Continuing Education Workshop.** Renton. Thursday-Saturday. Valley General Hospital. Contact: CME Harborview.

October 7-10—**Annual Meeting, Washington State Medical Association.** Yakima. Thursday-Sunday. Yakima Convention Center, The Towne Plaza, and The Holiday Inn. Contact: Marcia Wahlman, Convention Coordinator, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

November 11-12—**Topics in Emergency Medicine.** Seattle. Thursday-Friday. Sea-Tac Marriott Hotel. Contact: Heidi Hilby, Executive Secretary, Washington Chapter, American College of Emergency Physicians, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

WYOMING

June 30-July 3—**Wyoming Medical Society Annual Meeting.** Moran. Wednesday-Saturday. Jackson Lake Lodge. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne. WY 82001. (307) 635-2424.

See Washington listing, September 16-18, 1982.

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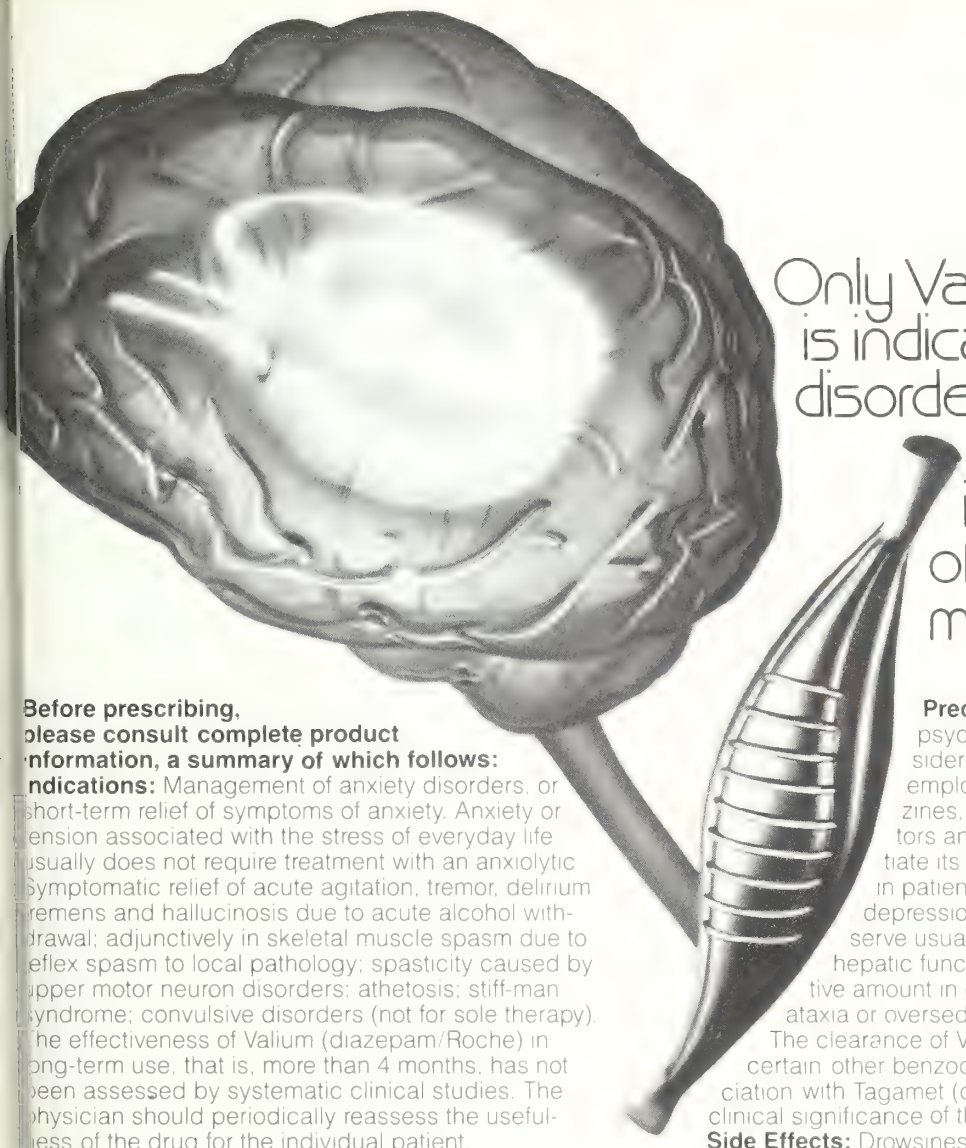

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

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Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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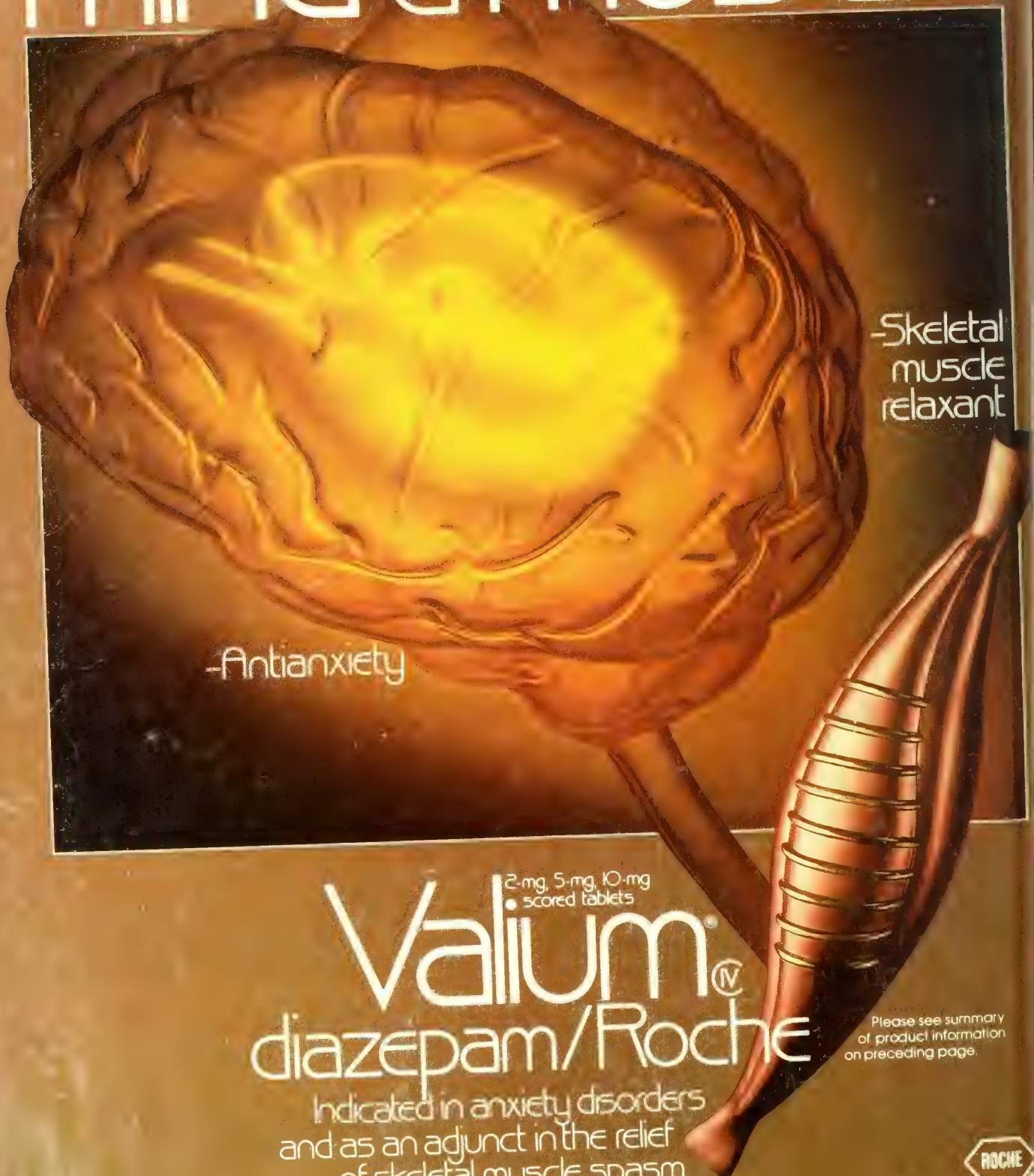

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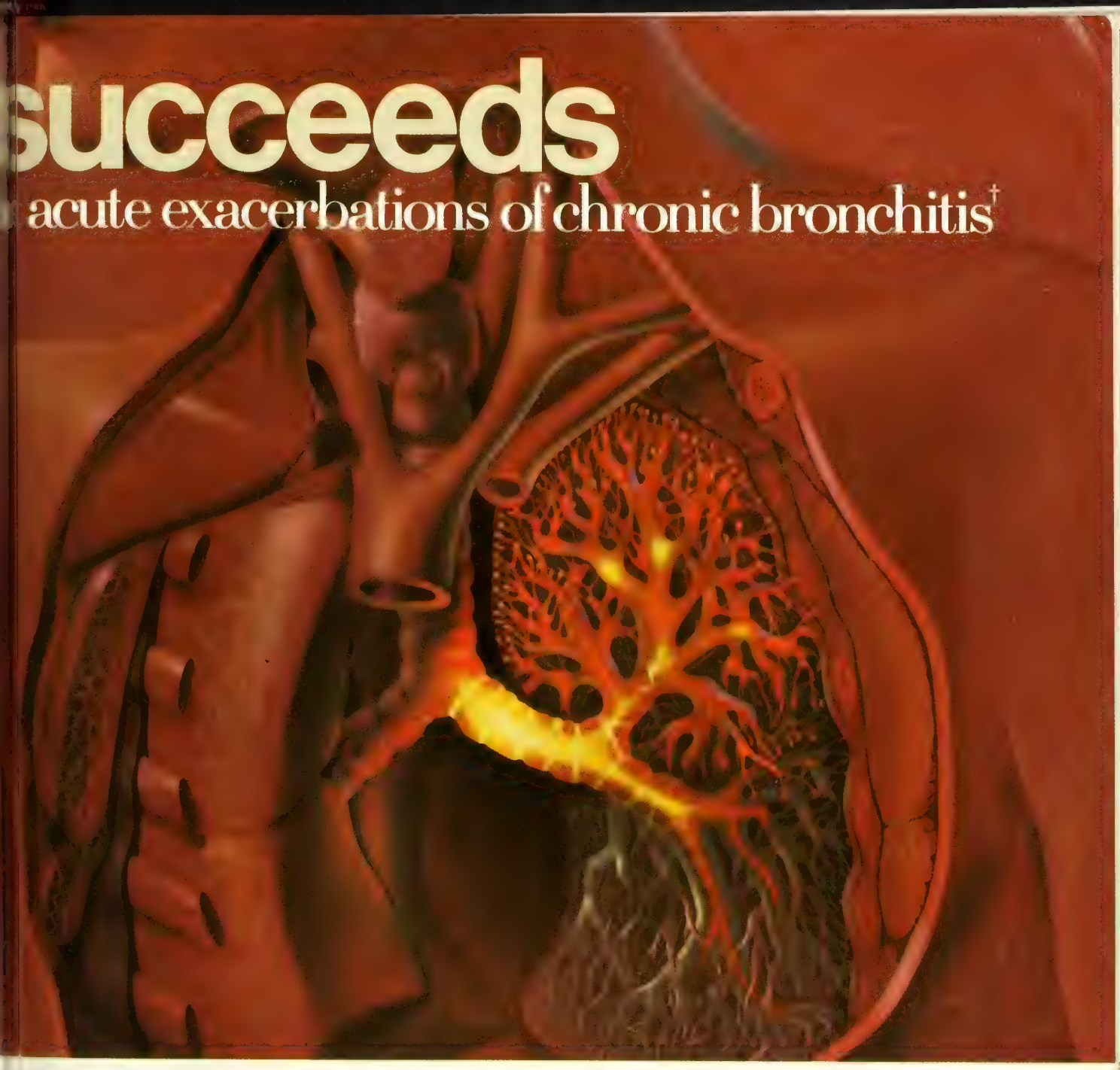

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Precautions: *General* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients. *Pregnancy* Teratogenic Effects Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

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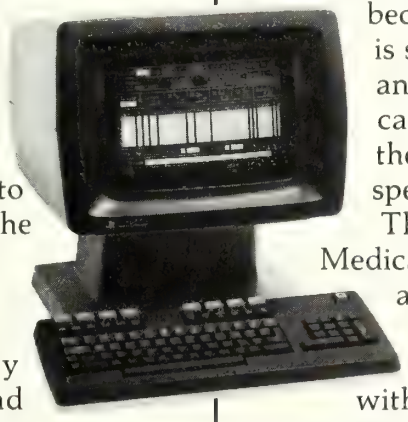

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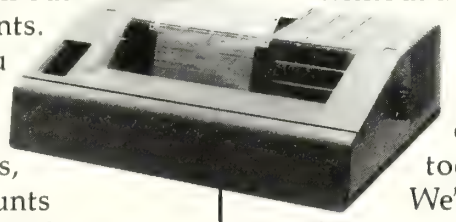

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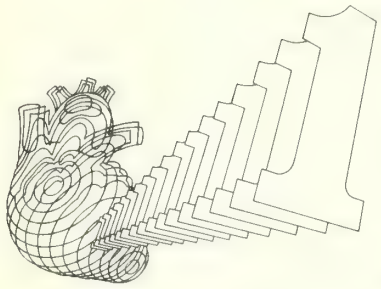

CORGARD®
nadolol tablets
40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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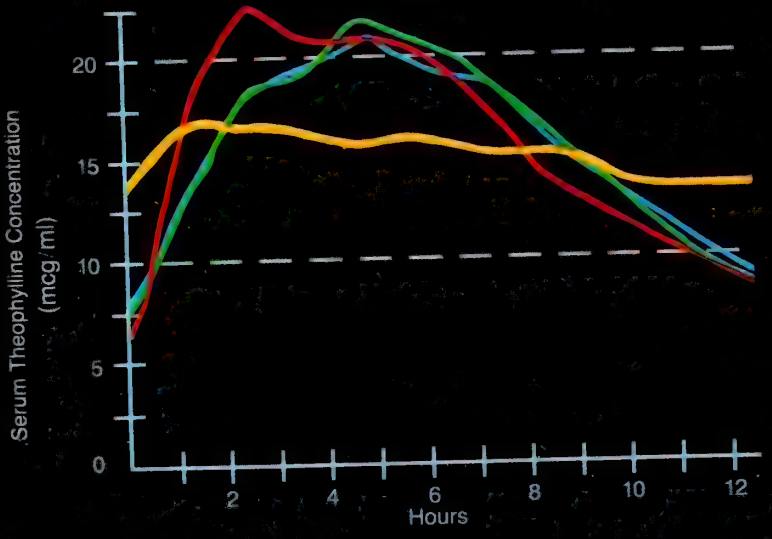

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Your patient benefits from the maximum control provided by THEO-DUR in several important ways: exercise tolerance is increased, emergency hospital visits are less likely and concomitant therapy is usually unnecessary.

Dosage titration is easy to achieve.* THEO-DUR is the only sustained action tablet in 200 mg as well as 100 and 300 mg strengths and all tablets are scored for greater dosage flexibility.

THEO-DUR also enhances patient compliance–with an every 12-hour dosage schedule that's easier to remember.

**After three days, on a steady dose, serum concentrations should be monitored and appropriate dosage adjustments made, if necessary.*

†*Adapted from Weinberger* et al: J Pediatr 99 *(no. 1): 145, July, 1981. Serum concentrations computer-projected from single dose absorption data in normal subjects supplied by the manufacturer or obtained experimentally (available on written request). Based on a rapid theophylline half-life of 3.7 hours, after achievement of steady-state levels with curves normalized to a concentration of 15 mcg/ml.*

Today's most widely prescribed bronchodilator.

THEO-DUR®

(anhydrous theophylline)

Sustained Action Tablets

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Please see next page for a summary of prescribing information.

THEO-DUR®

(anhydrous theophylline)

Sustained Action Tablets

Today's most widely prescribed bronchodilator.

Description: THEO-DUR Sustained Action Tablets contain anhydrous theophylline, with no color additives

Pharmacologic Actions: The pharmacologic actions of theophylline are as a bronchodilator, pulmonary vasodilator and smooth muscle relaxant since the drug directly relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels. Theophylline also possesses other actions typical of the xanthine derivatives: coronary vasodilator, diuretic, cardiac stimulant, cerebral stimulant and skeletal muscle stimulant. The actions of theophylline may be mediated through inhibition of phosphodiesterase and a resultant increase in intracellular cyclic AMP which could mediate smooth muscle relaxation.

Indications and Usage: Symptomatic relief and/or prevention of asthma and reversible bronchospasm associated with chronic bronchitis and emphysema

Contraindications: THEO-DUR is contraindicated in individuals who have shown hypersensitivity to any of its components or xanthine derivatives

Warnings: Excessive theophylline doses may be associated with toxicity; serum theophylline levels should be monitored to assure maximum benefit with minimum risk. Incidence of toxicity increases at serum levels greater than 20 mcg/ml. High blood levels of theophylline resulting from conventional doses are correlated with clinical manifestation of toxicity in: patients with lowered body plasma clearances, patients with liver dysfunction or chronic obstructive lung disease, and patients who are older than 55 years of age, particularly males. There are often no early signs of less serious theophylline toxicity such as nausea and restlessness, which may appear in up to 50% of patients prior to onset of convulsions. Ventricular arrhythmias or seizures may be the first signs of toxicity. Many patients who have higher theophylline serum levels exhibit a tachycardia. Theophylline products may worsen pre-existing arrhythmias

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established. This is, unfortunately, true for most anti-asthmatic medications. Therefore, use of theophylline in pregnant women should be balanced against the risk of uncontrolled asthma

Precautions: THEO-DUR TABLETS SHOULD NOT BE CHEWED OR CRUSHED. Theophyllines should not be administered concurrently with other xanthine medications. It should be used with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, and in the elderly, particularly males, and in neonates. Great caution should be used in giving theophylline to patients in congestive heart failure since these patients show markedly prolonged theophylline blood level curves. Use theophylline cautiously in patients with history of peptic ulcer. Theophylline may occasionally act as a local irritant to G.I. tract, although gastrointestinal symptoms are more commonly central and associated with high serum concentrations above 20 mcg/ml.

Adverse Reactions: The most consistent adverse reactions are usually due to overdose and are:
Gastrointestinal: Nausea, vomiting, epigastric pain, hematemesis, diarrhea.
Central Nervous System: Headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions
Cardiovascular: Palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, life threatening ventricular arrhythmias.
Respiratory: Tachypnea.
Renal: Albuminuria, increased excretion of renal tubular cells and red blood cells, potentiation of diuresis
Others: Hyperglycemia and inappropriate ADH syndrome

How Supplied: THEO-DUR 100 mg, 200 mg and 300 mg Sustained Action Tablets are available in bottles of 100, 500, 1000, and 5000, and in unit dose packages of 100

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For full prescribing information, see package insert

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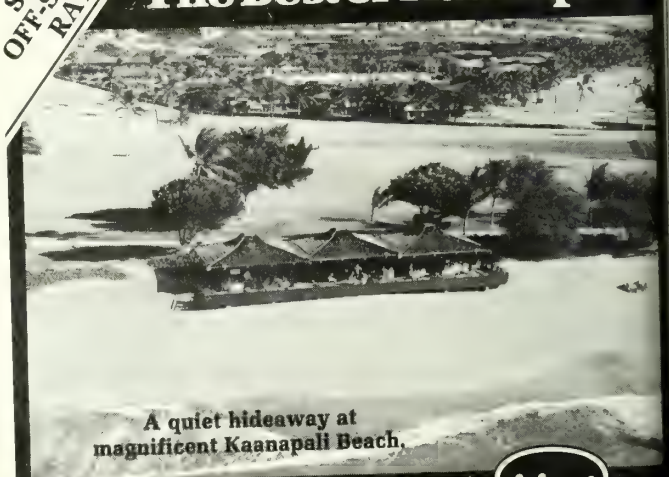

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An added complication... in the treatment of bacterial bronchitis*

Increasing incidence of ampicillin resistance in Haemophilus influenzae
Ampicillin Resistant Haemophilus influenzae
H. influenzae
S. pneumoniae

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy particularly to drugs

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coomb testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90).

As with other broad-spectrum antibiotics, colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with Ceclor.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor® (cefaclor). Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [100281R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.†

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

References

1. Antimicrob. Agents Chemother., *8*:91, 1975
2. Antimicrob. Agents Chemother., *11*:470, 1977.
3. Antimicrob. Agents Chemother., *13*:584, 1978.
4. Antimicrob. Agents Chemother., *12*:490, 1977.
5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II:880. Washington, D.C.: American Society for Microbiology, 1978
6. Antimicrob. Agents Chemother., *13*:861, 1978.
7. Data on file, Eli Lilly and Company
8. Principles and Practice of Infectious Diseases (edited by G.L. Mandell, R.G. Douglas, Jr., and J.E. Bennett), p. 487 New York: John Wiley & Sons, 1979

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

200066

INTRODUCING THE FIRST ONE-A-DAY ANTI-ARTHRITIC AGENT

Feldene®

(PIROXICAM) 20 mg capsules

ONE CAPSULE ONCE DAILY

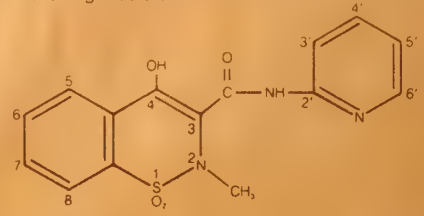
FOR OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

Please see next page for FELDENE (piroxicam) prescribing information

© 1982, Pfizer Inc.

FELDENE® CAPSULES
(piroxicam)
For Oral Use

DESCRIPTION. FELDENE (piroxicam) is 4-Hydroxy-2-methyl-*N*-2 pyridinyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, an oxicam. Members of the oxicam family are not carboxylic acids, but they are acidic by virtue of the enolic 4-hydroxy substituent. FELDENE occurs as a white crystalline solid, sparingly soluble in water, dilute acid and most organic solvents. It is slightly soluble in alcohols and in aqueous alkaline solution. It exhibits a weakly acidic 4-hydroxy proton (pKa 5.1) and a weakly basic pyridyl nitrogen (pKa 1.8). It has the following structure:



Molecular Formula: $C_{15}H_{13}N_3O_4S$ Molecular Weight: 331.35

CLINICAL PHARMACOLOGY. FELDENE has shown anti-inflammatory, analgesic and antipyretic properties in animals. Edema, erythema, tissue proliferation, fever, and pain can all be inhibited in laboratory animals by the administration of FELDENE. It is effective regardless of the etiology of the inflammation. The mode of action of FELDENE is not fully established at this time. However, a common mechanism for the above effects may exist in the ability of FELDENE to inhibit the biosynthesis of prostaglandins, known mediators of inflammation.

It is established that FELDENE does not act by stimulating the pituitary-adrenal axis.

FELDENE is well absorbed following oral administration. Drug plasma concentrations are proportional for 10 and 20 mg doses, generally peak within three to five hours after medication, and subsequently decline with a mean half-life of 50 hours (range of 30 to 86 hours, although values outside of this range have been encountered).

This prolonged half-life results in the maintenance of relatively stable plasma concentrations throughout the day on once daily doses and to significant drug accumulation upon multiple dosing. A single 20 mg dose generally produces peak piroxicam plasma levels of 1.5 to 2 mcg/ml, while maximum drug plasma concentrations, after repeated daily ingestion of 20 mg FELDENE, usually stabilize at 3-8 mcg/ml. Most patients approximate steady state plasma levels within 7 to 12 days. Higher levels, which approximate steady state at two to three weeks, have been observed in patients in whom longer plasma half-lives of piroxicam occurred.

FELDENE and its biotransformation products are excreted in urine and feces, with about twice as much appearing in the urine as the feces. Metabolism occurs by hydroxylation at the 5 position of the pyridyl side chain and conjugation of this product; by cyclodehydration; and by a sequence of reactions involving hydrolysis of the amide linkage, decarboxylation, ring contraction, and N-demethylation. Less than 5% of the daily dose is excreted unchanged.

Concurrent administration of aspirin (3900 mg/day) and FELDENE (20 mg/day), resulted in a reduction of plasma levels of piroxicam to about 80% of their normal values. The use of FELDENE in conjunction with aspirin is not recommended because data are inadequate to demonstrate that the combination produces greater improvement than that achieved with aspirin alone and the potential for adverse reactions is increased. Concomitant administration of antacids had no effect on FELDENE plasma levels. The effects of impaired renal function or hepatic disease on plasma levels have not been established.

FELDENE, like salicylates and other nonsteroidal anti-inflammatory agents, is associated with symptoms of gastrointestinal tract irritation (see ADVERSE REACTIONS). However, in a study utilizing ^{51}Cr-tagged red blood cells, 20 mg of FELDENE administered as a single dose for four days did not result in a significant increase in fecal blood loss and did not detectably affect the gastric mucosa. In the same study a total daily dose of 3900 mg of aspirin, i.e., 972 mg q.i.d., caused a significant increase in fecal blood loss and mucosal lesions as demonstrated by gastroscopy.

In controlled clinical trials, the effectiveness of FELDENE has been established for both acute exacerbations and long-term management of rheumatoid arthritis and osteoarthritis.

The therapeutic effects of FELDENE are evident early in the treatment of both diseases with a progressive increase in response over several (8-12) weeks. Efficacy is seen in terms of pain relief and, when present, subsidence of inflammation.

Doses of 20 mg/day FELDENE display a therapeutic effect comparable to therapeutic doses of aspirin, with a lower incidence of minor gastrointestinal effects and tinnitus.

FELDENE has been administered concomitantly with fixed doses of gold and corticosteroids. The existence of a "steroid-sparing" effect has not been adequately studied to date.

INDICATIONS AND USAGE. FELDENE is indicated for acute or long-term use in the relief of signs and symptoms of the following:

1. osteoarthritis
2. rheumatoid arthritis

Dosage recommendations for use in children have not been established.

CONTRAINDICATIONS. FELDENE should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other anti-inflammatory agents.

WARNINGS. In controlled clinical trials incidence of peptic ulceration with the maximum recommended FELDENE capsule dose of 20 mg/day was 0.8%. The use of doses higher than the recommended dose is associated with an increase in the incidence of gastrointestinal irritation and ulcers. As with other nonsteroidal anti-inflammatories, the administration of FELDENE to patients with a history of upper gastrointestinal tract disease should be closely supervised.

PRECAUTIONS. As with other anti-inflammatory agents, long-term administration to animals results in renal papillary necrosis and related pathology in rats, mice, and dogs.

As with other drugs that inhibit prostaglandin biosynthetase, reversible elevations of BUN have been reported in clinical studies with FELDENE. The effect is thought to result from inhibition of renal prostaglandin synthesis resulting in a change in medullary and deep cortical blood flow with an attendant effect on renal function. Because of the extensive renal excretion of piroxicam, patients with impaired renal function should be carefully monitored.

Although other non-steroidal anti-inflammatory drugs do not have the same direct effects on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when FELDENE is administered.

Because of reports of adverse eye findings with non-steroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

Less than 1.0% of patients receiving FELDENE (piroxicam) have shown reversible elevation of one or more liver function parameters. While concurrent aspirin may have been involved in some of these changes, a relationship to FELDENE could not be excluded. Studies in patients with impaired liver function have not been done.

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur (see CLINICAL PHARMACOLOGY), in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed. Therefore, these values should be determined if signs or symptoms of anemia occur.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, as with other nonsteroidal anti-inflammatory drugs, FELDENE should be used with caution in patients with compromised cardiac function, hypertension or other conditions predisposing to fluid retention.

DRUG INTERACTIONS. FELDENE is highly protein bound, and, therefore, might be expected to displace other protein-bound drugs. Although *in vitro* studies have shown this not to occur with dicoumarol, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels (see CLINICAL PHARMACOLOGY).

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam increased the incidence of dystocia and delayed parturition in pregnant animals when piroxicam administration was continued late into pregnancy. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to nonpregnant females or females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS. The incidence of adverse reactions to piroxicam is based on clinical trials involving approximately 2300 patients, about 400 of whom were treated for more than one year and 170 for more than two years. About 30% of all patients receiving daily doses of 20 mg of FELDENE experienced side effects. Gastrointestinal symptoms were the most prominent side effects—occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Other than the gastrointestinal symptoms, edema, dizziness, headache, changes in hematological parameters, and rash have been reported in a small percentage of patients. Routine ophthalmoscopy and slit-lamp examinations have revealed no evidence of ocular changes in 205 patients followed from 3 to 24 months while on therapy.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE at doses of 20 mg/day.

Incidence Greater Than 1% The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress*, nausea*, constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, and indigestion.

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), leucopenia, eosinophilia.

Urogenital: BUN elevations (see PRECAUTIONS).

Central Nervous System: dizziness, somnolence, vertigo.

Special Senses: tinnitus.

Body as a Whole: headache, malaise.

Cardiovascular/Respiratory: edema (see PRECAUTIONS).

Dermatologic: pruritus, rash.

*Reactions occurring in 3% to 6% of patients treated with FELDENE.

Incidence Less Than 1% (Causal Relationship Probable)
The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, dry mouth.

Hematological: thrombocytopenia.

Dermatologic: sweating, erythema, bruising, desquamation, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome.

Special Senses: swollen eyes, blurred vision, eye irritations.

Body as a Whole: pain (colic).

Cardiovascular/Respiratory: hypertension (see PRECAUTIONS).

Urogenital: hematuria.

Metabolic: hypoglycemia, weight increase, weight decrease.

Central Nervous System: depression, insomnia, nervousness.

Incidence Less Than 1% (Causal Relationship Unknown)
Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Cardiovascular/Respiratory: palpitations, dyspnea.

Central Nervous System: akathisia.

Urogenital System: dysuria.

OVERDOSAGE. In the event treatment for overdosage is required the long plasma half-life (see CLINICAL PHARMACOLOGY) of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendation of specific antidotal efficacy at this time. It is reasonable to assume, however, that the standard measures of gastric evacuation and general supportive therapy would apply.

ADMINISTRATION AND DOSAGE. Rheumatoid Arthritis, Osteoarthritis:
It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided. Because of the long half-life of FELDENE steady-state blood levels are not reached for 7-12 days. Therefore, although the therapeutic effects of FELDENE are evident early in treatment, there is a progressive increase in response over several weeks and the effect of therapy should not be assessed for two weeks.

Dosage recommendations and indications for use in children have not been established.

HOW SUPPLIED. FELDENE Capsules are available for oral administration as 10 mg (NDC 0069-3220-66) maroon and blue #322, and 20 mg (NDC 0069-3230-66) maroon #323: bottles of 100.

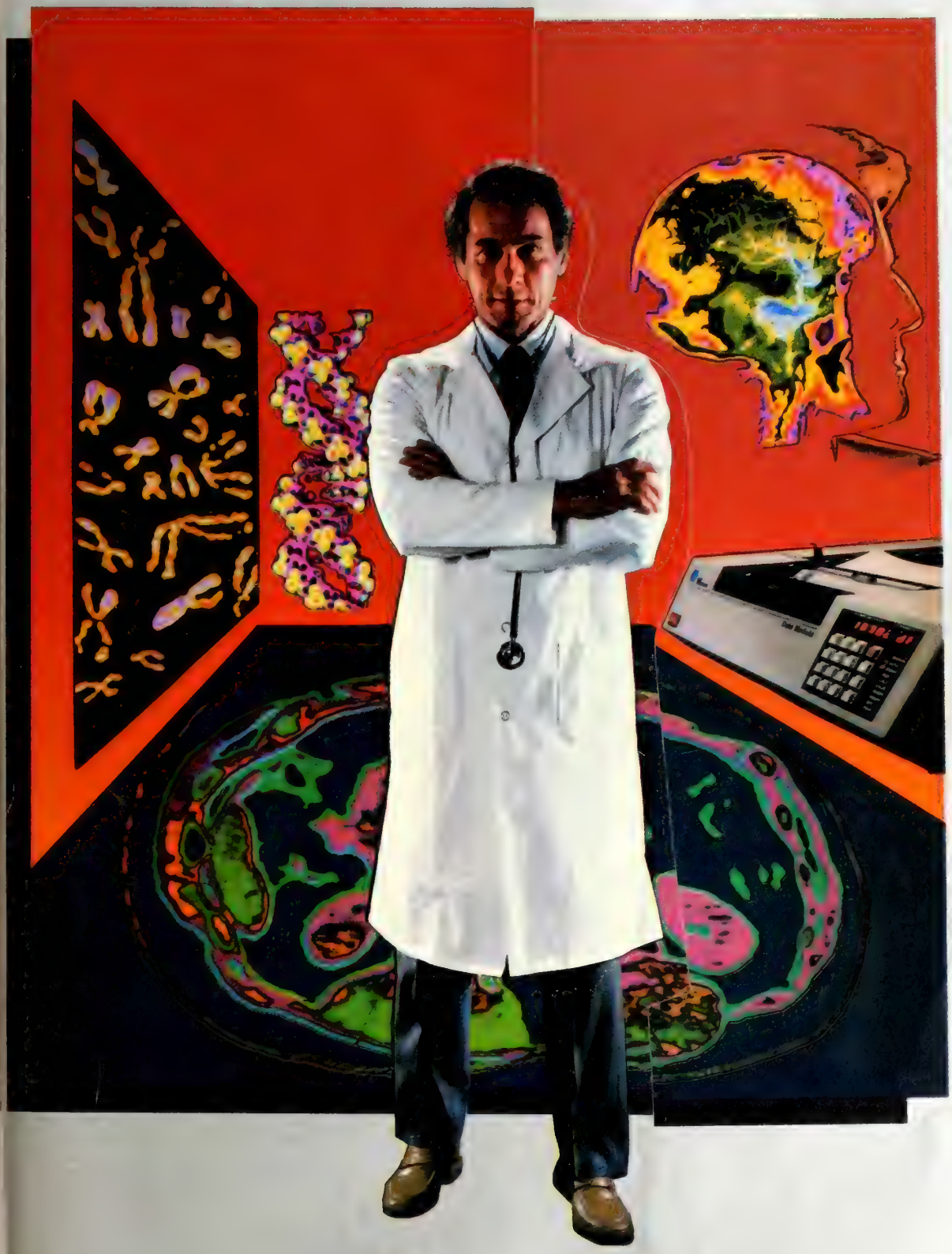
Unit dose 20 mg (NDC 0069-3230-41): packages of 100

Issued Apr. 19-

Pfizer LABORATORIES DIVISION
PFIZER INC

In an era of change,

An Agent of Change...



Your patients are changing

...the population is getting older, more peo are holding a second job, patients are mor concerned about the medications they tak

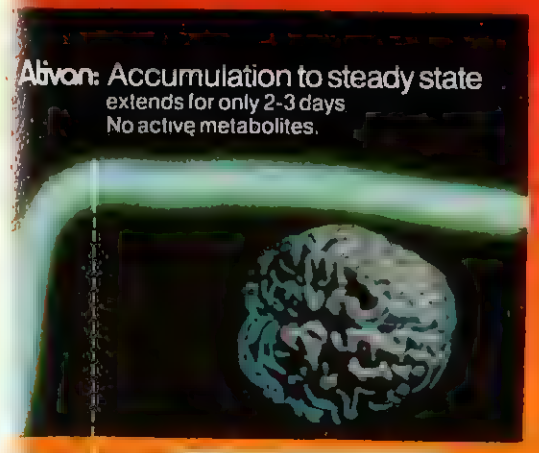
Medical knowledge is changing

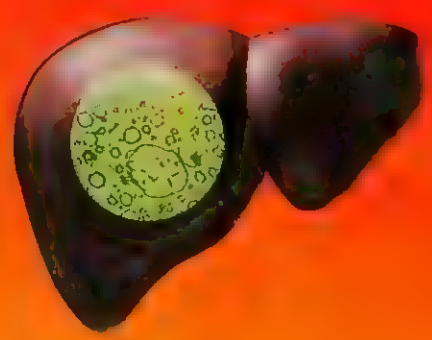
...there are diagnostic resources and surgical techniques undreamed of only a few years ago, biomedical engineering, new insights also into the action of drugs.

In this changing environment, the way you are practicing medicine is changing too...

Twenty years ago, the benzodiazepines represented a real step forward in the management of anxiety and tension states. In recent years, however, concern about drug accumulation and clearance has led physicians to re-evaluate their use of these agents. In light of current knowledge, many clinicians are changing from multi-metabolite benzodiazepines to Ativan® (lorazepam)—a metabolically and pharmacokinetically distinctive agent that offers clinical advantages which more closely meet the expectations of a modern anxiolytic.

Ativan®: Agent of Change
(lorazepam)





because...

it's shorter acting, with less accumulation*

In contrast to long-acting benzodiazepines, Ativan has a short, 12-hour half-life, and no active metabolites. In multiple-dose therapy, Ativan accumulates for only two to three days before reaching steady state; the long-acting benzodiazepines—diazepam CIV, chlordiazepoxide CIV, clorazepate CIV and flurazepam CIV—with their active metabolites—accumulate for as long as 20 days, increasing the likelihood of excessive sedation.

1. Klotz U, Reimann I: N Engl J Med *302*:1012-1014, 1980.
2. Desmond PV, Patwardhan RV, Schenker S, et al: Ann Intern Med *93*:266-268, 1980
3. Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology *79*:912-916, 1980
4. Sellers EM, Naranjo CA, Peachey JE. N Engl J Med *305*:1255-1262, 1981
5. Ruffalo RL, Thompson JF, Segal JL. South Med J *74*:1075-1078, 1981

*Pharmacokinetics cannot as yet be directly related to efficacy

†All benzodiazepines produce additive effects when given with CNS depressants such as barbiturates or alcohol

it doesn't interact with drugs metabolized by P450 microsomal enzymes

Most benzodiazepines undergo oxidative metabolism and thus utilize the hepatic microsomal enzyme system. Ativan® (lorazepam), however, is metabolized by glucuronidation and does not compete with other drugs for cytochrome P450. Thus, when Ativan is given with Tagamet® (cimetidine), for example, clearance is not delayed, nor sedation increased†—unlike reported observations with patients on other benzodiazepines.[1-5]

it gives you greater control of therapy

The short half-life of Ativan® facilitates more rapid response to dosage adjustments, allowing you to titrate therapy to patients' changing needs. Also, once you decide to discontinue Ativan, it will be out of your patient's system four days after the final dose—in contrast to long-acting benzodiazepines and their active metabolites which take as long as two weeks to be totally eliminated.

Ativan®
for (lorazepam) IV
Anxiety

See important information on following page.

Ativan®: Agent of Change
(lorazepam) ℞

- Little accumulation lessens likelihood of excessive sedation
- Unlike most benzodiazepines, Ativan does not compete with other drugs, such as Tagamet® (cimetidine), fo microsomal enzyme system during biotransformation
- Metabolism not affected by age or liver dysfunction
- Short half-life provides greater control of therapy
- Promptly eliminated from patient's system after discontinuation
- Specifically evaluated and found effective for anxiety associated with cardiovascular and gastrointestinal disorders
- A distinctive change from long-acting benzodiazepines, all of which have active metabolites and are much t same

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months

Precautions: In depression accompanying anxiety, consider possibility for suicide

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed

PREGNANCY: Reproductive studies were performed in mice, rats, a strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, me sals, malrotated limbs, gastroschisis, malformed skull and microphth were seen in drug-treated rabbits without relationship to dosage. Altho these anomalies were not present in the concurrent control group, they been reported to occur randomly in historical controls. At 40mg/k higher, there was evidence of fetal resorption and increased fetal loss i bits which was not seen at lower doses. Clinical significance of these fi is not known. However, increased risk of congenital malformations asso with use of minor tranquilizers (chlordiazepoxide, diazepam and mep mate) during first trimester of pregnancy has been suggested in severa ies. Because use of these drugs is rarely a matter of urgency, u lorazepam during this period should almost always be avoided. Possibili a woman of child-bearing potential may be pregnant at institution of th should be considered. Advise patients if they become pregnant to con cate with their physician about desirability of discontinuing the dr humans, blood levels from umbilical cord blood indicate placental tran lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in h milk like other benzodiazepines. As a general rule, nursing should n undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginn therapy and generally disappear on continued medication or on decr dose. In a sample of about 3,500 anxious patients, most frequent a reaction is sedation (15.9%), followed by dizziness (6.9%), weakness and unsteadiness (3.4%). Less frequent are disorientation, depressio sea, change in appetite, headache, sleep disturbance, agitation, derma cal symptoms, eye function disturbance, various gastrointestinal sym and autonomic manifestations. Incidence of sedation and unstea increased with age. Small decreases in blood pressure have been not are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear i multiple agents may have been taken. Manifestations of overdosage i somnolence, confusion and coma. Induce vomiting and/or undertake lavage followed by general supportive care, monitoring vital signs an observation. Hypotension, though unlikely, usually may be controlle Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has no determined.

Dosage: **Individualize for maximum beneficial effects. In dose gradually when needed, giving higher evening dose increasing daytime doses. Anxiety, usually 2-3mg/day given b t.i.d.; dosage may vary from 1 to 10mg/day in divided dose elderly or debilitated, initially 1-2mg/day; insomnia due to anx transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories Philadelphia, PA 19101

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ANESTHESIOLOGY

May 22-23—**Hemodynamic Monitoring/Pulmonary Artery Catheterization—Hands-on Workshops.** Calif. Soc. of Anesthesiologists and Stanford at Stanford. Saturday-Sunday. 15 hrs. $275, CSA members; $325, nonmembers. Contact: Educational Prog. Div., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

June 10-13—**California Society of Anesthesiologists—Annual Meeting.** Town and Country, San Diego. Thursday-Sunday. Contact: Educational Prog. Div., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

June 24-26—**Practical Closed Circuit Anesthesia II.** Pacific Medical Center at Hyatt at Union Square, San Francisco. Thursday-Saturday. 17 hrs. $300. Contact: Office of Cont. Ed., PMC, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

August 13-17—**Clinical Neuroanesthesia Workshop.** UCSD at La Jolla Village Inn, La Jolla. Friday-Tuesday. 24 hrs. $325.

August 21-22—**Hemodynamic Monitoring/Pulmonary Artery Catheterization—Hands-on Workshops.** Calif. Soc. of Anesthesiologists and Stanford at Stanford. Saturday-Sunday. 15 hrs. $275, CSA members; $325, nonmembers. Contact: Educational Prog. Div., CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

October 22-26—**American Society of Anesthesiologists.** Hilton, Las Vegas. Friday-Tuesday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

CANCER

June 18—**Symposium on Gynecologic Oncology.** Alta Bates Hospital, Berkeley. Friday. 7 hrs. $75. Contact: Med. Ed. Dept., Alta Bates Hosp., 3001 Colby St., Berkeley 94705. (415) 845-7110, ext. 2055.

October 1-2—**Advances in Heart Disease, Aging, Diabetes and Cancer Research.** See Medicine, October 1-2.

October 11-13—**Sixth Annual Cancer Symposium.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. $300. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

EMERGENCY MEDICINE

May 21-22—**Modern Concepts in Trauma Care.** Orange County Trauma Society and Mission Community Hospital at Disneyland Hotel, Anaheim. Friday-Saturday. 14 hrs. $195. Contact: John G. West, MD, Orange Co. Trauma Soc., 321 N. Rampart, Suite 120, Orange 92668. (714) 937-5030.

June 7-11—**Postgraduate Institute for Emergency Room Physicians—Symposium III.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs. $425.

June 28-July 2—**Topics in Emergency Medicine.** UCSF. Monday-Friday. 35 hrs. $350.

July 23-24—**Disaster Planning Symposium.** UCLA. Friday-Saturday.

July 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMA, Inc., 2310 Mason St., San Francisco 94133. (415) 956-5900.

August 9-13—**Postgraduate Institute for Emergency Room Physicians—Symposium II.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 36 hrs.

September 13-17—**Postgraduate Institute for Emergency Room**

(Continued on Page 27)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093 (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

BECAUSE A THIAZIDE ALONE CAN ONLY DO SO MUCH...

AND YET CAN DO TOO MUCH.

INCREASE CONTROL WITHOUT INCREASING POTASSIUM PROBLEMS.

A dependable means to long-term blood pressure control.

Many times, a diuretic alone can't keep hypertension in check. INDERIDE, however, can pick up where thiazide therapy leaves off.

The combination of propranolol HCl, the world's most trusted beta blocker, and hydrochlorothiazide, the standard among diuretics, enables INDERIDE to exert an additive antihypertensive effect.[1,2] In fact, a propranolol/hydrochlorothiazide regimen maintained blood pressure below 90 mm Hg in 81.8% to 86.4% of patients followed for 6 to 18 months of therapy.[1]

Low thiazide dosage means reduced risk of hypokalemia.

When thiazides are prescribed in doses greater than 50 mg/day, the potential for hypokalemia increases substantially. What's more, the greater the fall in serum K^+, the greater the risk of hypokalemia-induced PVCs.[3,4]

With INDERIDE, the additive hypotensive effect of propranolol HCl allows the effective dose of hydrochlorothiazide to be kept low (25 mg b.i.d.). And by lowering the daily dose of diuretic, INDERIDE also lowers the potential for diuretic-induced side effects. Potassium problems are less likely to occur—yet blood pressure can be controlled consistently.

INDERIDE®

Each tablet contains INDERAL® (propranolol HCl) 40 mg or 80 mg, and hydrochlorothiazide 25 mg

B.I.D. 40/25 80/25

When you know you need more than a thiazide.

Please see Brief Summary of Prescribing Information on following page.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERIDE®

BRAND OF propranolol hydrochloride (INDERAL®) and hydrochlorothiazide

No. 474—Each INDERIDE®-40/25 tablet contains	
Propranolol hydrochloride (INDERAL®)	40 mg
Hydrochlorothiazide	25 mg
No. 476—Each INDERIDE®-80/25 tablet contains	
Propranolol hydrochloride (INDERAL®)	80 mg
Hydrochlorothiazide	25 mg

WARNING: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

DESCRIPTION: INDERIDE combines two antihypertensive agents: INDERAL (propranolol hydrochloride), a beta-adrenergic blocking agent, and hydrochlorothiazide, a thiazide diuretic-antihypertensive.

INDICATION: INDERIDE is indicated in the management of hypertension. (See boxed warning.)

CONTRAINDICATIONS: Propranolol hydrochloride (INDERAL®): Propranolol hydrochloride is contraindicated in: 1) bronchial asthma, 2) allergic rhinitis during the pollen season, 3) sinus bradycardia and greater than first degree block, 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension, 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol, 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

Hydrochlorothiazide: Hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to this or other sulfonamide-derived drugs.

WARNINGS: Propranolol hydrochloride (INDERAL®): CARDIAC FAILURE. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely. a) If cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn. b) If tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA. Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. In patients with impaired renal function, cumulative effects of the drug may develop.

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

USE IN PREGNANCY: Propranolol hydrochloride (INDERAL®): The safe use of propranolol in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers. Thiazides appear in breast milk. If the use of the drug is deemed essential, the patient should stop nursing.

PRECAUTIONS: Propranolol hydrochloride (INDERAL®): Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements such as foods with a high potassium content.

Any chloride deficit is generally mild, and usually does not require specific treatment except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration, have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

ADVERSE REACTIONS: Propranolol hydrochloride (INDERAL®): *Cardiovascular* bradycardia, congestive heart failure, intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type, thrombocytopenic purpura.

Central Nervous System lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia; visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory bronchospasm.

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Hydrochlorothiazide: *Gastrointestinal* anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis.

Central Nervous System dizziness, vertigo, paresthesias, headache, xanthopsia.

Hematologic leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Cardiovascular orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactio

Other. hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

DOSAGE AND ADMINISTRATION: The dosage must be determined by individual titration (see boxed warning).

Hydrochlorothiazide is usually given at a dose of 50 to 100 mg per day. The initial dose of propranolol is 40 mg twice daily and it may be increased gradually until optimum blood pressure control is achieved. The usual effective dose is 160 to 480 mg per day.

One to two INDERIDE tablets twice daily can be used to administer up to 320 mg of propranolol and 100 mg of hydrochlorothiazide. For doses of propranolol greater than 320 mg, the combination products are not appropriate because their use would lead to an excessive dose of the thiazide component.

When necessary, another antihypertensive agent may be added gradually beginning with 50 percent of the usual recommended starting dose to avoid an excessive fall in blood pressure.

OVERDOSAGE OR EXAGGERATED RESPONSE: The propranolol hydrochloride (INDERAL) component may cause bradycardia, cardiac failure, hypotension, or bronchospasm.

The hydrochlorothiazide component can be expected to cause diuresis. Lethargy of varying degree may appear and may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function, and in the absence of significant serum electrolyte changes or dehydration. The mechanism of central nervous system depression with thiazide overdosage is unknown. Gastrointestinal irritation and hypermotility can occur; temporary elevation of BUN has been reported, and serum electrolyte changes could occur especially in patients with impairment of renal function.

TREATMENT: The following measures should be employed. GENERAL—If ingestion is, or may have been, recent, evacuate gastric contents taking care to prevent pulmonary aspiration. BRADYCARDIA—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. CARDIAC FAILURE—Digitalization and diuretics. HYPOTENSION—Vasopressors, *e.g.*, levarterenol or epinephrine. BRONCHOSPASM—Administer isoproterenol and aminophylline. STUPOR OR COMA—Administer supportive therapy as clinically warranted. GASTROINTESTINAL EFFECTS—Though usually of short duration, these may require symptomatic treatment. ABNORMALITIES IN BUN AND/OR SERUM ELECTROLYTES—Monitor serum electrolyte levels and renal function, institute supportive measures as required individually to maintain hydration, electrolyte balance, respiration, and cardiovascular-renal function.

HOW SUPPLIED: *No. 474*—Each INDERIDE®-40/25 tablet contains 40 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 476—Each INDERIDE®-80/25 tablet contains 80 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 and 1,000. Also in unit dose package of 100.

References: 1. Veterans Administration Cooperative Study Group on Antihypertensive Agents: J.A.M.A. *237*: 2303 (May 23) 1977. 2. Bravo, E.L., Tarazi, R.C., and Dustan, H.P.: N. Engl. J. Med. *292*: 66 (Jan. 9) 1975. 3. Hollifield, J.W., and Slaton, P.E.: Acta Med. Scand. [Suppl.] *647*: 67, 1981. 4. Holland, O.B., Nixon, J.V., and Kuhnert, L.: Am. J. Med. *70*: 762 (Apr.) 1981.

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(Continued from Page 23)

Physicians—Symposium I. UCSD at Vacation Village, San Diego. Monday-Friday. 36 hrs.

September 28-October 1—**American College of Emergency Physicians.** San Francisco. Tuesday-Friday. Contact: ACEP, 3900 Capital City Blvd., Lansing, MI 48906.

October 11-15—**Emergency Medicine.** USC. Monday-Friday.

October 11-15—**Postgraduate Institute for Emergency Room Physicians—Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 36 hrs.

October 22-24—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates, Inc., at Ralph W. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMA, 2310 Mason St., San Francisco 94133. (415) 956-5900.

October 25-29—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 35 hrs. $350.

December 13-17—**Postgraduate Institute for Emergency Room Physicians—Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 33 hrs. $425.

MEDICINE

May 15—**Memory Loss—An Increasing Clinical Problem.** See Psychiatry, May 15.

May 15-18—**American Thoracic Society—Annual Scientific Meeting.** Bonaventure Hotel, Los Angeles. Saturday-Tuesday. 30 hrs. $35, members; $100, nonmembers. Contact: S. R. Iannotta, Exec. Dir., ATS, 1740 Broadway, New York 10019. (212) 245-8000.

May 17-21—**Advances in Internal Medicine.** UCSF. Monday-Friday. 40 hrs. $375.

May 21-22—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

May 22-23—**Practical Management of Infectious Diseases for the Primary Care Physician.** UCLA. Saturday-Sunday. 9 hrs. $175.

May 27-30—**4th Annual Refresher Course in Allergy and Asthma.** UCD at Marriott's Great America, Santa Clara. Thursday-Sunday. 20 hrs. $250.

June 7-9—**Clinical Echocardiography—1982: M-Mode, 2-Dimensional and Pulse Doppler Techniques.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Monday-Wednesday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 9—**Bleeding Disorders.** LLU. Wednesday. 4 hrs. $30.

June 11-13—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Aladdin Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

June 25-27—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Newporter Inn, Newport Beach. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

July 10-18—**30th Annual Intensive Review of Internal Medicine.** USC. 9 days

July 16-17—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

July 17-24—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 21 hrs. $325.

August 6-8—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Clouds-Cal Neva Resort, Lake Tahoe. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 13-15—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 20-22—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at Hyatt, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 30-September 4—**Fifth Comprehensive Nephrology Review Course.** UCLA at Marriott, Los Angeles. Monday-Saturday. 28½ hrs. $595.

September 16-18—**4th Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Thursday-Saturday.

September 30-October 2—**Pulmonary Update.** UCSF. Thursday-Saturday.

October 1-2—**Advances in Heart Disease, Aging, Diabetes and Cancer Research.** UCLA at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Robert J. Morin, MD, Harbor-UCLA Medical Center, Torrance 90509. (213) 533-2233.

October 2-3—**The Skin from A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Saturday-Sunday.

October 6-10—**American Academy for Cerebral Palsy and Developmental Medicine—36th Annual Meeting.** Sheraton Harbor Island, San Diego. Wednesday-Sunday. 26 hrs. Contact: Kevin Johns, Convention Mgr., P.O. Box 11083, Richmond, VA 23230. (804) 355-9529.

October 9-16—**Gastroenterology.** USC at Mauna Kea Beach Hotel, Kamuela. One week.

October 18-25—**Pulmonary Medicine 1982: Advances and American Board Review.** USC at Hilton, Pasadena. One week.

October 21-23—**California Society of Internal Medicine—Annual Meeting.** MGM Grand, Reno. Thursday-Saturday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103.

November 11-14—**Allergy/Immunology: Practical Aspects Today and Into the 21st Century.** American Assn. for Clinical Immunology and Allergy at Marriott, Anaheim. Thursday-Sunday. 30 hrs. $250. Contact: Howard S. Silber, Exec. Dir., AACIA, P.O. Box 912-DTS, Omaha, NE 68101. (402) 551-0801.

December 8—**Chronic Diarrhea—Its Diagnosis and Treatment.** LLU. Wednesday.

OBSTETRICS AND GYNECOLOGY

May 19-21—**Perinatal Medicine: Issues and Impact.** Mount Zion Hospital and Medical Center at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday. Contact: Office of Cont. Ed., Mount Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

May 22—**Breast-Feeding in the 80s: Recent Developments and Current Views.** See Pediatrics, May 22.

June 2-5—**Controversies in Obstetrics and Gynecology.** Memorial Hospital Medical Center-UCI Center for Health Education at Silverado Country Club, Napa. Wednesday-Saturday. 20 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

September 8—**Current Concepts in Menopausal and Post-Menopausal Care.** LLU. Wednesday.

October 10-15—**Reproductive Health Care—Changing Concepts in Fertility Regulation.** Wayne State University at Marriott, Maui. Sunday-Friday. Contact: E. S. E. Hafez, Dept. of Obstetrics/Gynecology, Wayne State Univ., Sch. of Med., Med. Research Bldg., Rm 416, 5500 E. Canfield, Detroit 28201. (313) 577-1011.

October 11-15—**OB/GYN Review.** USC at Hilton, Pasadena. Monday-Friday. $450.

PEDIATRICS

May 19—**Los Angeles Pediatric Society—Annual Spring Meeting.** Hilton, Los Angeles. Wednesday. 2 hrs. $20. Contact: Eve Black, Exec. Sec., P.O Box 2022, Inglewood 90305. (213) 757-1198.

May 22—**Breast-Feeding in the 80s: Recent Developments and Current Views.** UCLA. Saturday. 7 hrs. $65.

May 29-31—**Challenges in Pediatrics.** Northern California Chapter, American Academy of Pediatrics, at Monterey. Saturday-Monday. Contact: David A. Zlotnick, MD, 3200 Middlefield Rd., Palo Alto 94306.

July 11-12—**First Annual Disneyland Pediatric Seminar.** American Academy of Pediatrics, Calif. Chap. 2, at Disneyland Hotel, Anaheim. Sunday-Monday. 12 hrs. Contact: AAP, Calif. Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

September 29-30—**39th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Hilton, Los Angeles. Wednesday-Thursday. 11 hrs. $145, members; $175, nonmembers. Contact: Eve Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

November 10—**Pediatric Emergencies.** LLU. Wednesday.

November 19-22—**Clinical Pediatrics.** Calif. Chapters 1,2,3, American Academy of Pediatrics, at Hilton, Las Vegas. Friday-Monday. 14 hrs. $195, members; $220, nonmembers. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

PSYCHIATRY

May 15—**Memory Loss—An Increasing Clinical Problem.** UCLA. Saturday. 6 hrs. $85.

June 3-5—**Depression.** UCD at Del Monte Hyatt, Monterey. Thursday-Saturday. 10 hrs. $20.

June 21-25—**The Management of Contemporary Problems in Private Psychiatry.** USC at Vacation Village, San Diego. Monday-Friday. 21 hrs. $250.

June 25-26—**Medical Aspects of Sexual Orientation: Medical and Psychological Issues.** See Of Interest to All, June 25-26.

October 9-10—**Sexual Deviation: Contemporary Psychoanalytic Views.** So. Calif. Psychoanalytic Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Contact: Mrs. Carol Ziff, Exec. Sec., SCPS, 9024 Olympic Blvd., Beverly Hills 90211. (213) 936-2877.

December 9-12—**American Academy of Psychoanalysis—26th Winter Meeting.** Hotel del Coronado, Coronado. Thursday-Sunday. 20 hrs. Contact: Vivian Mendelsohn, Admin. Dir., 30 E. 40th St., Suite 608, New York 10016. (212) 679-4105.

RADIOLOGY AND PATHOLOGY

June 11-13—**Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza, Los Angeles. Friday-Sunday. 17 hrs. Contact: Carl Perry, MD, Los Angeles Radiological Soc., 201 S. Alvarado, Suite 311, Los Angeles 90057. (213) 484-5120.

June 20-25—**Pathology of the Lung.** UCSD at La Jolla Village Inn, La Jolla. Sunday-Friday. 50 hrs.

July 24-30—**Laboratory Medicine.** USC at Maui Marriott Resort, Maui. One week. 27 hrs. $435.

August 7-14—**Radiology.** USC at Mauna Kea Beach Hotel, Kamuela. One week.

August 30-September 1—**Napa Valley Radiology Conference.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at Napa Valley. Monday-Wednesday. 18 hrs. $275. Contact: Michael H. Reid, PhD, MD, Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

September 11—**Ninth Annual Radiology Symposium.** So. Calif. Permanente Medical Group and Kaiser Foundation Hospitals at Beverly Hilton, Beverly Hills. Saturday. Contact: Doris McMath, SCPMG, Regional Dept. of Education and Research, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 25—**Clinical Ultrasound in Obstetrics and the Neonatal Period.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at Sacramento. Saturday. 6 hrs. $75. Contact: J. P. McGahan, MD, Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

October 7-10—**Society of Nuclear Medicine—7th Annual Western Regional Meeting.** Town and Country Hotel, San Diego. Thursday-Sunday. Contact: Jean Parker, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

October 9-17—**7th Annual International Body Imaging Conference.** West Park Hospital at Sheraton Royal Waikoloa Hotel, Kona, Hawaii. One week. 28 hrs. $385. Contact: Conference Secretary, Dept. of Radiology, West Park Hosp., 22141 Roscoe Blvd., Canoga Park 91304. (213) 340-0580, ext. 280.

December 2-4—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. 23 hrs. Contact: Luis M. de la Maza, MD, PhD, Dept. of Pathology, UCI Medical Center, Orange 92668. (714) 634-6868.

December 5-7—**Leucocyte Conference.** USC at Asilomar, Pacific Grove. Sunday-Tuesday.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section. UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

May 21-22—**Modern Concepts in Trauma Care.** Orange County Trauma Society and Mission Community Hospital at Disneyland Hotel, Anaheim. Friday-Saturday. 14 hrs. $195. John G. West, MD, Orange Co. Trauma Soc., 321 N. Rampart, Suite 120, Orange 92668. (714) 937-5030.

June 2-4—**OTO 83.** Project HEAR at Hyatt Regency, San Fran-

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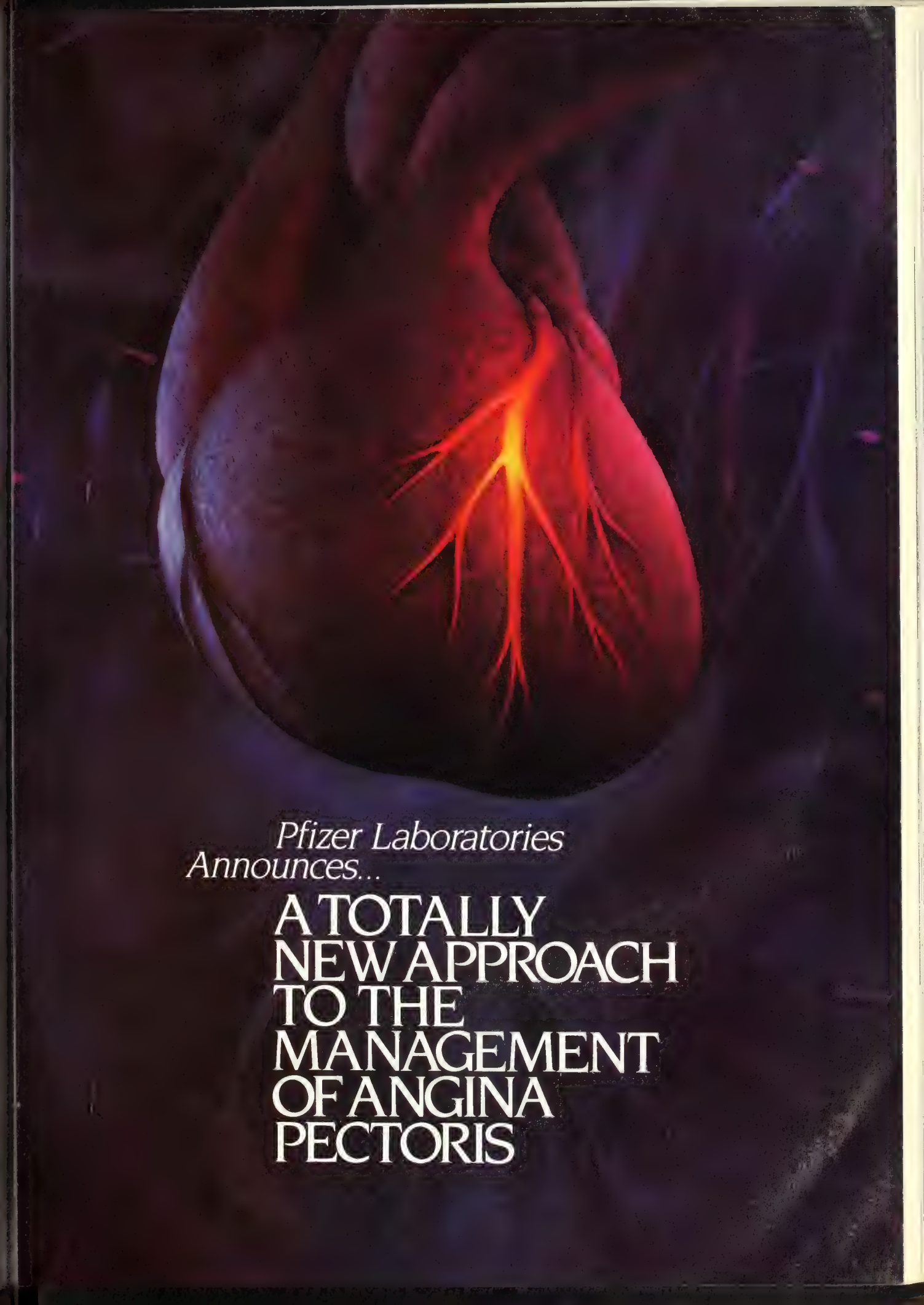
Pfizer Laboratories
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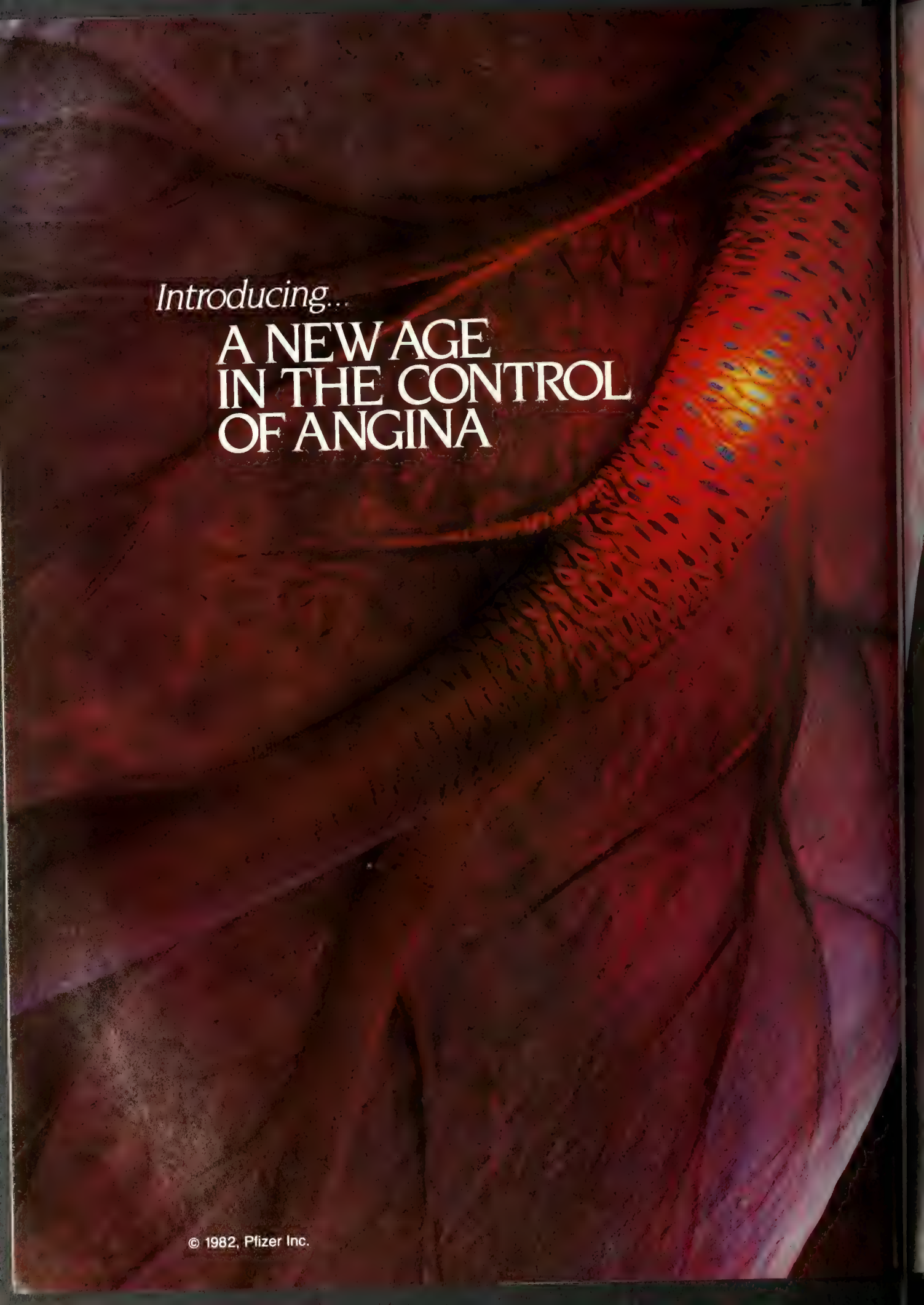
A TOTALLY
NEW APPROACH
TO THE
MANAGEMENT
OF ANGINA
PECTORIS



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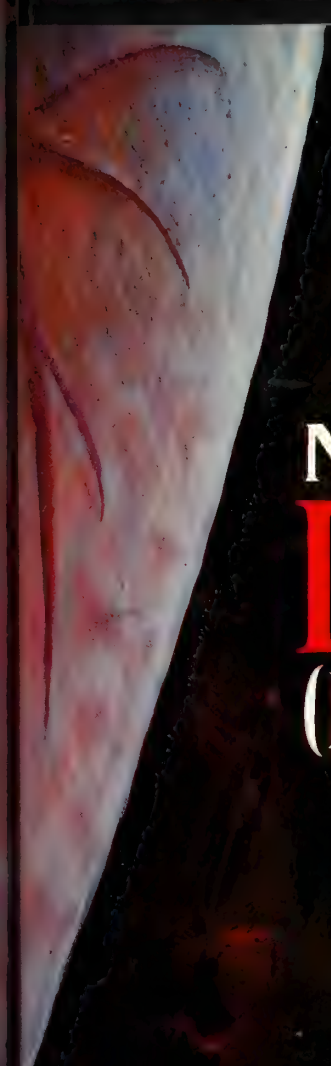


NEW PROCARDIA® (NIFEDIPINE) *Capsules 10 mg*

PROCARDIA is the beginning of a new age in the treatment of angina.

The Calcium Age.

It is now known that calcium ions, working at the cellular level, regulate the degree of vasoconstriction and, thereby, play a critical role in the anginal attack.

PROCARDIA acts at the cell membrane to selectively block calcium access to the contractile process in the arterial cell.

Through this action, PROCARDIA manages:

—vasospastic angina by dilating coronary arteries to increase myocardial O_2 supply and preventing coronary artery spasm

—classical effort-associated angina by dilating peripheral arteries to reduce afterload and myocardial O_2 demand

—mixed angina which involves elements of vasospastic and effort-associated angina

Like beta blockers, PROCARDIA reduces myocardial O_2 demand. But, unlike these agents, PROCARDIA also increases myocardial O_2 supply to both normal and poststenotic areas[1] of the myocardium and also prevents coronary artery spasm.

PROCARDIA®

THE FIRST ORAL CALCIUM CHANNEL BLOCKER

Please see PROCARDIA Brief Summary on last page.

NEW PROCARDIA® (NIFEDIPINE) *Capsules 10 mg*

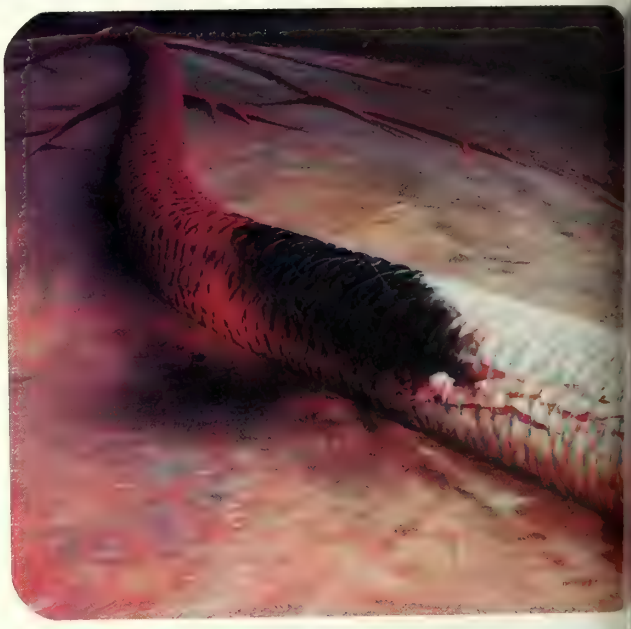
PROVEN EFFECTIVE ACROSS THE SPECTRUM OF ANGINA

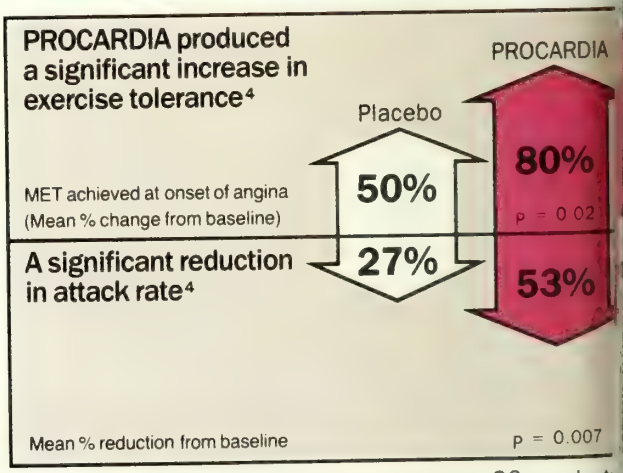
Contemporary medical opinion holds that the pathophysiology of angina is a spectrum ranging from pure, fixed atherosclerotic lesion to pure coronary artery spasm. Many patients, however, are believed to have a combination of both lesion and spasm.[2,3]

Angina due to pure fixed lesion can be prevented by reducing oxygen demand. Angina due to coronary artery spasm can be treated by preventing the spasm itself, thereby increasing oxygen supply. With this new understanding of angina, optimal antianginal therapy should provide this dual action: increasing O_2 supply while reducing O_2 demand.

In effort angina*

(when symptomatic despite conventional therap



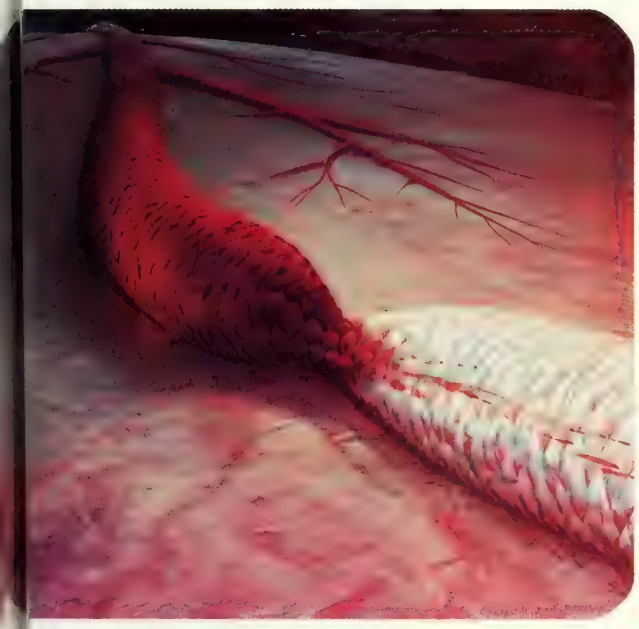


Double-blind, placebo-controlled, crossover 20-week st of 32 patients (27 evaluated for attack rate; 19 for exe tolerance). Mean PROCARDIA dosage: 51 mg/day.

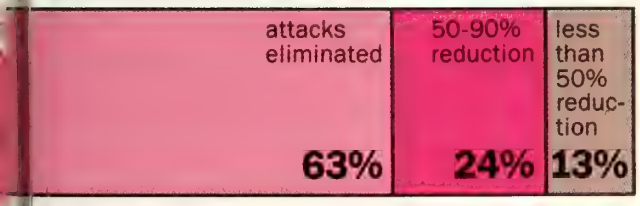
*In chronic stable angina (effort-associated angina) PROCAR has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exerc tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomp

Please see PROCARDIA Brief Summary on last page

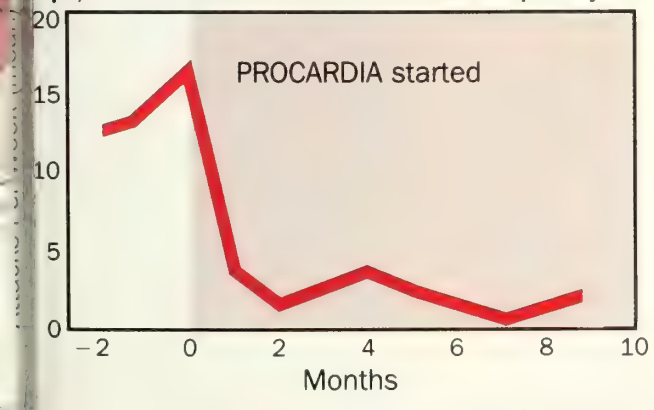
vasospastic angina



PROCARDIA eliminated attacks in 63% of patients[5]

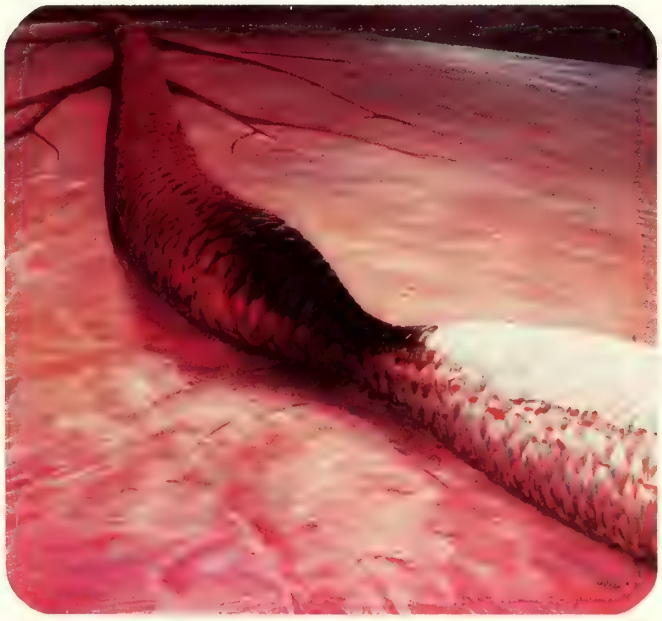


mpt, sustained decrease in attack frequency[5]



-term, open study of 127 patients unresponsive to beta kers and/or nitrates with symptoms of myocardial emia and demonstrated coronary artery spasm. CARDIA dosage: 40 to 160 mg/day.

In mixed angina (fixed lesion and spasm)



PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed.

PROCARDIA®

THE FIRST ORAL CALCIUM CHANNEL BLOCKER

NEW PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

ANGINA MANAGEMENT BEYOND BETA BLOCKERS

—Beta blockers prevent angina primarily by lowering myocardial oxygen demand. Like these agents, PROCARDIA reduces myocardial oxygen demand. However, PROCARDIA provides an added dimension of angina control by increasing myocardial oxygen supply where coronary artery spasm is present.

—Beta blockers can actually cause spasm. PROCARDIA prevents spasm.

—Beta blockers decrease myocardial perfusion in poststenotic areas. PROCARDIA increases myocardial perfusion to both normal and poststenotic areas.

—Beta-blocker treatment is limited in patients with myocardial dysfunction, COPD, asthma, bundle branch blocks, and diabetes. PROCARDIA can be given safely in all these groups of patients.

—The hypotensive effect of PROCARDIA is usually modest and well tolerated, however, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or subsequent upward dosage adjustment, and may be more likely with concomitant beta blockers.

—Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA, or at the time of dosage increases. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers, if possible, rather than stopping them abruptly before beginning PROCARDIA.

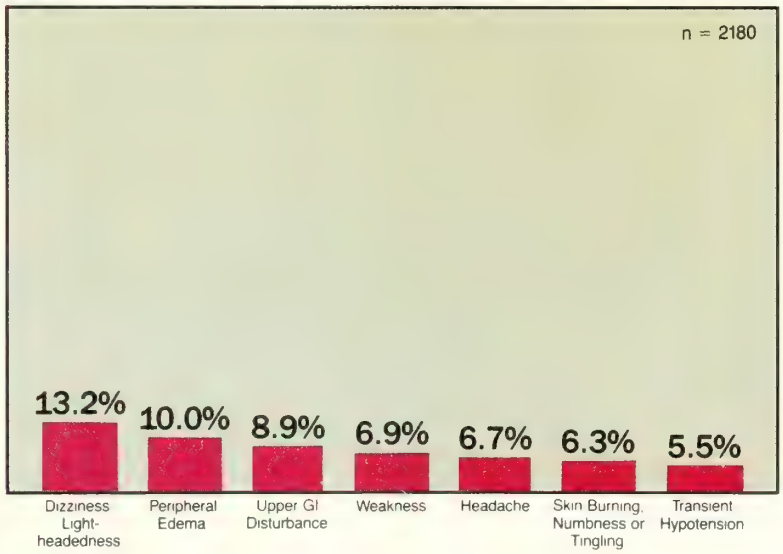
—Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

Please see PROCARDIA Brief Summary on last page

THE FIRST ORAL CALCIUM CHANNEL BLOCKER...

PROVIDES PROTECTION WITH A MILD SIDE-EFFECT PROFILE

Most common adverse reactions



Information is drawn from a large uncontrolled experience in 2180 patients and presents the most frequent side effects reported with PROCARDIA.

AN ADDED ADVANTAGE: COMPATIBILITY

—MAY BE USED WITH A WIDE VARIETY OF OTHER AGENTS

—CAN BE USED WITH NITRATES AND BETA BLOCKERS WITH CAUTION (See Warnings and Precautions)

THE FIRST ORAL CALCIUM CHANNEL BLOCKER FOR THE MANAGEMENT OF ANGINA

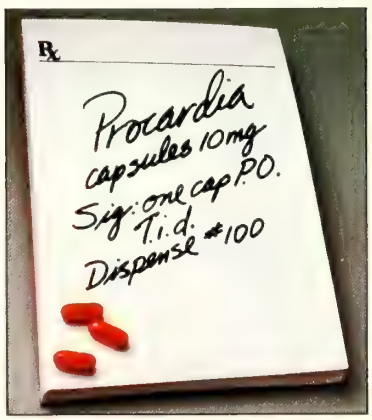
NEW PROCARDIA® (NIFEDIPINE) *Capsules 10 mg*

Proven effective when used alone.

Enhanced effectiveness when combined with beta blockers.

Convenient dosing

Start with:	1	10-mg capsule *t.i.d.*
Titrate to:	2	10-mg capsules *t.i.d.*
Titrate to:	3	10-mg capsules *t.i.d*



For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g. 3 days) if symptoms warrant and the patient is observed closely. Maximum dose 180 mg/day

References

1. Lichtlen PR, Engel H-J, Wolf R, et al. Regional myocardial blood flow in patients with coronary artery disease after nifedipine. In Lichtlen PR, Kimura E, Taira N (eds). *International Adalat® Panel Discussion. New Experimental and Clinical Results*. Tokyo, Excerpta Medica, 1978, pp 69–85.
2. Maseri A, Chierchia S. Angina pectoris—a new dimension, a new approach. Part 2. *Primary Cardiol* 6:123–136, October 1980.
3. Braunwald E. *Introduction. New Concepts in Ischemic Heart Disease. The Role of Coronary Artery Spasm*. New York, Science & Medicine, Inc, 1980, p 1.
4. Mueller HS, Chahine RA. Interim report of multicenter double-blind, placebo-controlled studies of nifedipine in chronic stable angina. *Am J Med* 71:645-657, October 1981.
5. Antman E, Muller J, Goldberg S, et al. Nifedipine therapy for coronary-artery spasm: experience in 127 patients. *N Engl J Med* 302:1269–1273, June 5, 1980.

PROCARDIA® CAPSULES

For Oral Use

(nifedipine)

BRIEF SUMMARY

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effect of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate the peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Pregnancy: Category C.

ADVERSE REACTIONS: The most common adverse events include dizziness, light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contains 10 mg of nifedipine. PROCARDIA Capsules are supplied in amber glass bottles of 100 capsules (NDC 0069-2600-66).

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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Pfizer LABORATORIES DIVISION
PFIZER INC

(Continued from Page 28)

cisco. Wednesday-Friday. 24 hrs. Contact: Project HEAR, 1801 Page Mill Rd., Palo Alto 94304. (415) 494-2000.

June 3-4—**12th Annual Neurosurgery Postgraduate Course.** UCSF at Hilton, San Francisco. Thursday-Friday. 16 hrs. $250.

June 4-6—**Traumatic Brain Injury: A Multidisciplinary Approach to Acute and Chronic Treatment.** UCD at El Rancho Racquet Resort, Sacramento. Friday-Sunday. 20 hrs. $210.

June 5-8—**Intensive Course in Refractive Keratoplasty: Barraquer Technique.** Jules Stein Eye Institute, Los Angeles Saturday-Tuesday. 32 hrs. $1,750. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

June 17-19—**Cosmetic Blepharoplasty Workshop.** Jules Stein Eye Institute, Los Angeles. Thursday-Saturday. 24 hrs. $250. Contact: Lu Hendricks, JSEI, UCLA School of Medicine, Center for Health Sciences, Los Angeles 90024. (213) 825-4617.

June 19-26—**Medical and Surgical Management of Ocular Inflammation.** USC at Mauna Kea Beach Hotel, Kamuela. One week. 26½ hrs. $435.

August 11—**Back Pain.** LLU. Wednesday.

August 12-14—**Selection and Technique for Use of Muscle and Musculocutaneous Flaps in Reconstructive Surgery.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 20 hrs. $420.

August 14-25—**Update: Surgery 1982.** USC at Sheraton Waikiki, Honolulu, and Maui Marriott Resort, Maui. 12 days. 35 hrs. $425.

September 12-25—**Temporal Bone Surgical Dissection Course.** House Ear Institute, Los Angeles. Two weeks. 100 hrs. $1,500. Contact: Antonio De La Cruz, MD, House Ear Inst., 256 S. Lake St., Los Angeles 90057.

September 29-October 1—**New Concepts in Maxillofacial Surgery.** STAN and Swiss Assn. for the Study of Internal Fixation at Stanford. Wednesday-Friday. 17 hrs. Contact: ASIF Course Secretariat, P.O. Box 514, Wayne, PA 19087. (215) 293-0654.

October 1-2—**Intraocular Lens Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA School of Medicine, Center for Health Sciences, Los Angeles 90024. (213) 825-4617.

October 10-15—**Annual Meeting of American Society of Plastic and Reconstructive Surgeons, Plastic Surgery Educational Foundation, American Society of Maxillofacial Surgeons.** Sheraton Waikiki, Honolulu. Sunday-Friday. 30 hrs. Contact: Linda Campbell, Dept. of Meetings Management, ASPRS, 233 N. Michigan Ave., Suite 1900, Chicago 60601. (312) 856-1818.

October 13—**Post-Operative Complications—Their Prevention and Management.** LLU. Wednesday.

October 15-16—**Advanced Seminar in Urologic Surgery.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

October 16-23—**4th International Seminar on Operative Arthroscopy.** UCLA at Maui. One week. 38 hrs. $785 with labs; $685, without.

October 30—**Diagnosis and Treatment of Nasal Disorders.** UCSD. Saturday.

October 30-November 5—**American Academy of Ophthalmology.** Moscone Convention Center, San Francisco. One week. Contact: AAO, P.O. Box 7424, San Francisco 94115. (415) 921-4700.

November 4-6—**Sterling Bunnell Memorial Lectureship.** UCSF (Dept. of Orthopaedic Surgery). Thursday-Saturday.

November 28-December 10—**Temporal Bone Surgical Dissection Course.** House Ear Institute, Los Angeles. Two weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, House Ear Inst., 256 S. Lake St., Los Angeles 90057.

December 4—**Photocoagulation Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $250. Contact: Lu Hendricks, JSEI, UCLA School of Medicine, Center for Health Education, Los Angeles 90024. (213) 825-4617.

OF INTEREST TO ALL PHYSICIANS

May 15-16—**Chronic Low Back Pain—The Causes and Successful Management.** UCLA. Saturday-Sunday. 10 hrs. $135.

May 15-16—**Hypnosis for Primary Care Physicians (Intermediate Level Course).** Alta Bates Hospital, Berkeley. Saturday-Sunday. 14 hrs. $170. Contact: Med. Ed. Dept., Alta Bates Hosp., 3001 Colby St., Berkeley 94705. (415) 845-7110, ext. 2055.

May 22-23—**New Dimensions in Stress Management.** UCLA. Saturday-Sunday. 10 hrs. $175.

May 22-23—**Conference on Health Problems Related to the Chinese in America.** Chinese Hospital and UCSF at Holiday Inn/Financial District, San Francisco. Saturday-Sunday. 12 hrs. $85. Contact: Elizabeth S. Weston, Chinese Hosp., 845 Jackson St., San Francisco 94133. (415) 982-2400, ext. 215.

May 31—June 4—**9th Annual Joint UCLA-Santa Monica Hospital Medical Center Family Practice Refresher Course.** Miramar-Sheraton, Santa Monica. Monday-Friday. 35 hrs. Contact: UCLA.

June 5—**The Medical Consequences of Nuclear War: Rx for Prevention.** UCSD at Civic Center, San Diego. Saturday. 6 hrs. $45.

June 9-11—**7th Annual Conference: Clinical Application of Hyperbaric Oxygen.** Memorial Hospital Medical Center at Disneyland Hotel, Anaheim. Wednesday-Friday. 24 hrs. Contact: Baromedical Dept., Memorial Hosp. Med Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3613.

June 14-19—**UCI Family Practice Refresher Course.** Marriott, Newport Beach. Sunday-Friday. 50-56 hrs.

June 25-26—**Medical Aspects of Sexual Orientation: Medical and Psychological Issues.** Bay Area Physicians for Human Rights at San Francisco Medical Society Building, San Francisco. Friday-Saturday. 10 hrs. Contact: James Krajeski, MD, 2001 Union St., San Francisco 94123. (415) 673-3189.

June 26—**Binge Eating and Purging: Recognition and Management of Bulimia.** UCLA. Saturday. 6 hrs. $80.

July 6-8—**Family Practice Board Review Course.** UCSF. Tuesday-Thursday.

July 9-11—**Sensory Systems' Influence on Movement and Tone—10th Annual Sensorimotor Integration Symposium.** UCSD at Holiday Inn at the Embarcadero, San Diego. Friday-Sunday.

July 14—**Special Problems in Geriatric Medicine.** LLU. Wednesday. 4 hrs.

July 25-29—**National Medical Association—87th Annual Convention and Scientific Assembly.** Hilton, San Francisco. Sunday-Thursday. 40 hrs. Contact: Christine C. Miller, Dir. of Prog. Operations, NMA, 1301 Pennsylvania Ave., NW, Washington, DC 20001. (202) 347-8598.

August 12-13—**National Institute for Care of the Elderly.** Univ. of Nevada-Reno School of Medicine at MGM Grand, Reno. Thursday-Friday. 12 hrs. Contact: Leanne Stone, Cont. Ed., Univ. of Nevada-Reno, Reno 89557. (702) 784-4046.

August 13-14—**6th Annual Sports Medicine Conference.** Univ. of Nevada-Reno School of Medicine at MGM Grand, Reno.

(Continued on Page 56)

In Hypertension*...When You Need to Conserve K^+

Every Step of the Way

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide', although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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Carolina, P.R. 00630

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THE WESTERN
Journal of Medicine

Refer to: Mahler RJ, Romanoff NE, Dunbar A, et al: The dilemma of defining diabetes mellitus in the aging population. West J Med 1982 May; 136:379-383

The Dilemma of Defining Diabetes Mellitus in the Aging Population

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A total of 1,009 persons were given a 100-gram glucose solution orally after a three-day regimen of a diet preparation and an overnight fast. Fasting and two-hour plasma glucose levels were determined for each subject and the results tabulated. Most of the persons tested were in the sixth, seventh or eighth decade of life with 43 persons between 80 and 89 years of age. The frequency of fasting plasma glucose determinations above 140 mg per dl varied from 3 percent to 7 percent between the sixth and ninth decades. Those persons with two-hour plasma glucose values above 200 mg per dl represented 8 percent of the 50 to 59 year old group and the percentages rose respectively to 12 percent, 16 percent and 21 percent in the 60 to 69, 70 to 79 and 80 to 89 year old groups. Finally, those who had fasting plasma glucose levels below 140 mg per dl and two-hour glucose values between 140 and 200 mg per dl were tabulated according to decade of life. This group varied from 9 percent to 15 percent between ages 20 and 59 and represented 20 percent to 22 percent of those in the seventh, eighth and ninth decades. In light of the known deterioration of glucose tolerance with aging, some stratification of blood glucose concentrations should be applied with age, but to what degree and what diagnostic criteria should be applied are still unclear.

RAPIDLY EXPANDING KNOWLEDGE concerning the pathogenesis of diabetes mellitus has led to an increased awareness of the need to revise the nomenclature, diagnostic criteria and classification of diabetes. The recognition of a lack of uniformity in defining diabetes mellitus and other categories of glucose intolerance led to the establishment of a workshop for creating an international classification system. The results and recommendations of the workshop have been published by the National Diabetes Data Group of National Institutes of Health.[1] The aims of the workshop were to establish a classification of diabetes that would serve as a framework for the collection of epidemiologic data on the etiology, natural history and impact of diabetes and its complications in diverse populations. The workshop further sought to "aid the clinician in cate-

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ABBREVIATION USED IN TEXT

OGTT = oral glucose tolerance test

gorizing and managing patients who have various degrees of glucose intolerance or who possess characteristics which place them at increased risk of developing diabetes."[1(p1040)]

One requirement of the terminology and classification system was to be able to place an individual at any time throughout life in only one class (although that person may subsequently require reclassification) so that each class would contain a population as homogeneous as possible. Further, the system was to use only simple clinical measurements or descriptive observations that are readily obtainable and have biologic significance.

Recognizing that the diagnosis of diabetes mellitus in an aging population has become increasingly more meaningful in recent decades, we have focused our attention on this aspect. Although it is well accepted that glucose tolerance deteriorates with age, the precise criteria to be applied at each decade of life and the relationship between these criteria and the sequelae of diabetes mellitus in the aging population remain unresolved.[2-12]

The specific criteria for establishing the diagnosis of diabetes mellitus, according to the National Diabetes Data Group, require that a 75-gram glucose load be given and that the fasting plasma glucose level must be above 140 mg per dl on two separate tests or that the two-hour post-glucose-load value exceed 200 mg per dl on two separate tests with one other measurement before the two-hour point being over 200 mg per dl on two separate tests as well. In the present study, a 100-gram oral glucose load was administered and a single venous plasma glucose level determined in the fasting state and two hours following the glucose load. Therefore the methods applied in the present study and practiced for the past five years are not strictly comparable with the criteria established by the National Diabetes Data Group for the diagnosis of diabetes mellitus. Nevertheless, we considered it worthwhile to apply the criteria of elevated fasting plasma glucose values above 140 mg per dl and two-hour post-glucose-load values greater than 200 mg per dl to the population studied to establish the frequency of glucose abnormalities by decades in a population skewed toward older age groups.

TABLE 1.—*Profile of Subjects Tested, With Distribution by Sex and Decade of Life*

Number in Category	*Ages*	*Men*	*Women*
62	20-29	17	45
70	30-39	21	49
71	40-49	23	48
154	50-59	52	102
377	60-69	146	231
232	70-79	96	136
43	80-89	23	20
TOTAL 1,009		378	631

Methods and Subjects

The data presented are the results of studies conducted during semiannual "Diabetes Detection Drives" held at the Eisenhower Medical Center, Rancho Mirage, California. All subjects were screened to exclude people known to have diabetes. A diet consisting of 150 to 300 grams of carbohydrate was provided for three days before the test. On the morning of the test, after an overnight fast, a venous blood specimen was collected for glucose level determination. Immediately thereafter a 100-gram oral glucose solution was given and ingested within ten minutes. Exactly two hours later, a second specimen of venous blood was collected. All blood specimens were put into fluoridated vacutainers to limit glycolysis during the interim between sampling and analysis and all specimens were analyzed within eight hours of collection. All glucose level determinations were carried out on plasma by a Beckman System 1 using the glucose oxidase method.

Results

Table 1 shows the total number of patients studied, grouped according to sex and decade of life. Of note is the predominant age distribution in the sixth, seventh and eighth decades with a representative sampling of octogenarians as well. This demographic distribution represents the age distribution of the retirement community in which the hospital is located and, though unique nationally, may be characteristic of the age distribution of other retirement communities.

Table 2 shows by decade the frequency of fasting plasma glucose determinations above 140 mg per dl. Of interest is the abrupt increase beyond the 50th year, which stabilizes between 2 percent and 4 percent up to the eighth decade.

TABLE 2.—*Subjects With Fasting Plasma Glucose (FPG) Levels Over 140 mg per dl, With Distribution by Sex and Decade of Life*

Ages	Number in Category	FPG > 140 mg/dl Number	Percentage	Men Number	Women Number
20-29	62	..	..	..	..
30-39	70	..	..	..	..
40-49	71	..	..	..	..
50-59	154	3	2	1	2
60-69	377	15	4	11	4
70-79	232	5	2	2	3
80-89	43	3	7	..	3
TOTAL	1,009	26	3	14	12

TABLE 3.—*Two-Hour Plasma Glucose (PG) Levels Above 200 mg per dl Following 100-Gram Oral Glucose Load, With Distribution by Sex and Decade of Life*

Ages	Number in Category	2 hr Postprandial PG > 200 mg/dl Number	Percentage	Men Number	Women Number
20-29	62	..	..	..	..
30-39	70	..	..	..	..
40-49	71	..	..	..	..
50-59	154	12	8	6	6
60-69	377	47	12	24	23
70-79	232	37	16	10	27
80-89	43	9	21	2	7
TOTAL	1,009	105	10	42	63

TABLE 4.—*Subjects With Fasting Plasma Glucose (FPG) Level Under 140 mg per dl and Two-Hour Plasma Glucose Over 200 mg per dl, Distribution by Decade of Life*

Ages	Number	FPG < 140 mg/dl 2 hr PP > 200 mg/dl Number	Percentage
20-29	62	..	..
30-39	70	..	..
40-49	71	..	..
50-59	154	10	6.5
60-69	377	31	8.2
70-79	232	33	14.2
80-89	43	6	14.0
TOTAL	1,009	80	7.9

TABLE 5.—*Subjects With Fasting Plasma Glucose (FPG) Levels Below 140 mg per dl and Two-Hour Plasma Glucose Levels Between 140 and 200 mg per dl, With Distribution by Sex and Decade of Life*

Ages	Number in Category	FPG < 140 mg/dl 2 hr > 140 mg/dl but < 200 mg/dl Number	Percentage	Men Number	Women Number
20-29	62	9	15	3	6
30-39	70	6	9	2	4
40-49	71	9	13	3	6
50-59	154	22	14	4	18
60-69	377	77	20	31	46
70-79	232	52	22	26	26
80-89	43	9	21	5	4
TOTAL	1,009	184	18	74	110

The seeming increase in frequency in the 80 to 89 years age group must be interpreted with caution in view of the small number of subjects found to be abnormal in that age group. Chi-square analysis of all patients younger than 60 (357 patients) as compared with those over 60 years (652 patients) showed a statistically increased frequency of fasting plasma glucose levels above 140 mg per dl ($P<.01$) in the group older than 60 years.

Table 3 shows the surprisingly high frequency of elevated two-hour serum glucose determinations of 200 mg per dl and above occurring in an ascending manner in the 60 to 69, 70 to 79 and 80 to 89 year old age groups.

Table 4 lists those subjects by decade who had fasting plasma glucose values below 140 mg per dl and two-hour plasma glucose levels above 200 mg per dl. There was an increasing frequency of this divergence in each decade over age 50. Chi-square analysis of all patients under 60 years old (227 patients) as compared with those over 60 years (652 patients) showed a statistically increased frequency of patients with fasting plasma glucose values below 140 mg per dl and two-hour plasma glucose values above 200 mg per dl in those subjects 60 years of age and older ($P<.005$).

Table 5 presents those subjects with fasting plasma glucose levels below 140 mg per dl and a two-hour plasma glucose concentration between 140 and 200 mg per dl. At each decade, the results were found to equal or exceed the frequency of abnormal values found with observation of either fasting glucose or two-hour glucose levels over 200 mg per dl (Table 3).

Discussion

Almost 60 years after Hagedorn's initial efforts at defining normality of glucose tolerance, there still exists no unanimity of opinion concerning the interpretation of glucose tolerance tests in aging people.[3] One reason for this lack of agreement is the fact that there is no clear division between diabetic and nondiabetic populations in either fasting or two-hour oral glucose tolerance test (OGTT) blood glucose levels. Rather, the frequency distribution in a representative population shows a continuous unimodal distribution from low to high, skewed to the higher level.[13] Consequently, no features of the curve allow patients with diabetes to be distinguished from those without diabetes. This is in contrast to the Pima

Indian population and the Western Samoan-Polynesian population, where one finds a bimodal distribution between the nondiabetic and diabetic populations—that is, two-hour plasma glucose level below 200 mg per dl defining the nondiabetic population and falling in the first mode, whereas diabetic patients with two-hour levels above 200 mg per dl fall in the second mode.[14-16] Moreover, the observation that diabetic sequelae of retinopathy and nephropathy are confined to those subjects with two-hour plasma glucose levels above 200 mg per dl gives clinical credence to this natural subdivision of the diabetic from the nondiabetic Pima Indian and Western Samoan-Polynesian populations. As an extension of these observations, there has been a tendency by some to arbitrarily define all subjects in the general population with two-hour plasma glucose values above 200 mg per dl as having diabetes mellitus.

Compounding the problem of a necessarily arbitrary selection of numbers with which one is to define the diabetic population is the fact that, in general, glucose tolerance seems to decrease with age. Although a number of possibilities have been proposed to explain the mechanism or mechanisms for this phenomenon, the critical question exists as to whether the decline in performance that occurs with aging should be considered a general adaptive process affecting most of the population—in which case standards for normality should be further age adjusted—or whether the decline in tolerance is caused by the progressive selective evolution of increasing numbers of people with true diabetes—in which case age adjustment would be inappropriate.[13]

In support of the former position is the realization that failure to readjust postglucose values with age would result in the diagnosis of diabetes mellitus in up to 75 percent of certain populations tested, leading in fact to general condemnation of the glucose tolerance test by some investigators.[17] The alternative point of view, that the increasing number of abnormal glucose values with age represents a selection of the true diabetic population, is supported by the observation that some diabetic sequelae, particularly cardiovascular disease and retinopathy, are seen more commonly in aging hyperglycemic patients as compared with aging normoglycemic people.[14,18,19]

Some stratification of glucose measurements should be applied with age but the question exists as to what criteria should be applied and to what degree. In a critical review of this subject, O'Sullivan[8] takes the position that the role of diagnostic standards should take precedence over age effects for their contribution to the frequency of abnormal tests. In agreement with O'Sullivan, it would seem that there is no valid reason for discounting the influence of age on blood glucose standards simply because they might give rise to "unacceptably" high prevalence rates. There is general agreement that what is needed is the documentation of the health significance of the standards adopted. In other words, do the criteria established to diagnose the presence of diabetes mellitus correlate with the clinical development of vascular complications from the disease? Rushforth, Miller and Bennett[20] have looked at this question in the Pima Indians, a population group with a distinct bimodal distribution of fasting and two-hour plasma glucose level abnormalities. Only the hyperglycemic group showed a higher prevalence of retinopathy and nephropathy, suggesting that this group does indeed constitute those with diabetes mellitus.[20-22] Additionally, Jarrett and Keen[23] found that the risk of specific diabetic complications became important only in people with capillary whole blood glucose concentrations exceeding 200 mg per dl two hours after a 50-gram oral glucose load and those who had overnight fasting blood glucose concentrations exceeding 110 mg per dl. These obervations appear to refute the suggestion by Siperstein[17] that it is unlikely that subtle degrees of glucose intolerance would have any deleterious effect on tissue capillaries. Consequently, abnormal fasting and two-hour postprandial plasma glucose values seen in aging people is not a benign process and does bear clinical relevance as a predictive indicator for those patients in whom vascular complications are more likely to develop.

If one attempts to apply simple criteria to the establishment of the diagnosis of diabetes mellitus in aging, then fasting plasma glucose and two-hour OGTT values seem to be pertinent. Based on the results obtained with 1,009 subjects, an elevated fasting plasma glucose level of 140 mg per dl and above occurred in approximately 5 percent of subjects from the sixth through the eighth decades, with a small and insignificant rise to 7 percent in the ninth decade. Hence, a fasting plasma glucose value above 140 mg per dl probably constitutes a valid means of diagnosing the presence of diabetes mellitus through the ninth decade of life. This is in

good agreement with the data of O'Sullivan[8] who found a trivial increase in fasting plasma glucose levels with age, averaging 1 to 2 mg per dl each decade.

A two-hour OGTT value above 200 mg per dl also seems to be a valid indicator of abnormality diagnostic of diabetes mellitus at any age even though, as evident in this report, there is a statistically increased frequency of elevated two-hour glucose values above 200 mg per dl beyond the age of 59. For reasons explained previously, we accept that a finding of a two-hour plasma glucose level over 200 mg per dl, regardless of age, should always be considered abnormal.[8,24]

Finally, it has been variously reported that after a 100-gram oral glucose load, the two-hour plasma glucose level will rise at a rate of from 6 to 13 mg per dl each decade.[3,8] If one accepts a value below 140 mg per dl as normal for younger populations, the criterion most commonly employed by the US Public Health Service,[25] Fajans and Conn,[26] the British Diabetic Association[27] and the World Health Organization,[28] then it seemed appropriate to determine the number of subjects encompassed in the present report with two-hour plasma glucose values between 140 and 200 mg per dl (see Table 5). Interestingly, the figure varied from 9 percent to 20 percent from the third through the sixth decade and then remained fairly constant at 20 percent to 22 percent during the seventh, eighth and ninth decades. These are subjects to whom the terms *borderline* or *chemical* diabetes would apply but that, in view of the ambiguities caused by their advancing age, we would not choose to identify as abnormal at at present. Rather, we would agree with recent comments by Davidson that "Because of the social and employment as well as the insurance ramifications of labeling a patient diabetic, the diagnosis should be avoided" in this group until the clinical significance of this borderline abnormality of glucose tolerance is resolved.[4(p699)]

REFERENCES

1. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979; 28:1039-1057

2. Niejadlik DC: The glucose tolerance test—An evaluation. Postgrad Med 1974 Jun; 55:73-78

3. Andres R: Aging and diabetes. Med Clin North Am 1971 Jul; 55:835-846

4. Davidson MB: The effect of aging on carbohydrate metabolism—A review of the English literature and a practical approach to the diagnosis of diabetes mellitus in the elderly. Metabolism 1979 Jun; 28:688-705

5. Houser HB, Mackay W, Verma N, et al: A three-year controlled follow-up study of persons identified in a mass screening program for diabetes. Diabetes 1977 Jul; 26:619-627

6. Kawate R, Miyanishi M, Nishimoto Y: Prevalence and mortality of diabetes mellitus in Japanese in Hawaii and Japan, *In* Baba S, Goto Y, Fukui I (Eds): Diabetes Mellitus in Asia. Amsterdam, Excepta Medica 1976, pp 82-90

7. O'Connor ML: Glucose tolerance test—How you can make it more reliable. Nursing 1975; 7:10-11

8. O'Sullivan JB: Age gradient in blood glucose levels—Magnitude and clinical implications. Diabetes 1974 Aug; 23:713-715

9. Phillips PJ, Pain RW: Rationalizing the diagnosis of diabetes mellitus. Med J Aust 1977 Mar 12; 1:380-381

10. Shagan BP: Diabetes in the elderly patient. Med Clin North Am 1976; 60(6):1191-1208

11. Sherwin RS: Limitations of the oral glucose tolerance test in diagnosis of early diabetes. Primary Care 1977 Jun; 4(2):255-266

12. Moss JM: Pitfalls to avoid in diagnosing diabetes in elderly patients. Geriatrics 1976 Oct; 31:52-55

13. National Center for Health Statistics, US Public Health Service Series 11, 1964, No. 2

14. Bennett PH, Rushforth NB, Miller M, et al: Epidemiologic studies of diabetes in the Pima Indians. Recent Prog Horm Res 1976; 32:333-376

15. Hamman RF, Bennett PH, Miller M: Incidence of diabetes among the Pima Indians. Adv Metab Disord 1978; 9:49-63

16. Zimmet P: Epidemiology of diabetes and its macrovascular manifestations in Pacific populations: The medical effects of social progress. Diabetes Care 1979 Mar-Apr; 2:144-153

17. Siperstein MD: The glucose tolerance test: A pitfall in the diagnosis of diabetes mellitus. Adv Intern Med 1975; 20:297-323

18. Butterfield WJH: Summary of results of the Bedford Diabetes Survey. Proc R Soc Med 1962; 57:196

19. Jackson WP, Vinik AI: Hyperglycemia and diabetes in the elderly, *In* Ellenberg M, Rifkin H (Eds): Diabetes Mellitus: Theory and Practice. New York, McGraw-Hill, 1970, pp 526-545

20. Rushforth NB, Miller M, Bennett PH: Fasting and two-hour post-load glucose levels for the diagnosis of diabetes—The relationship between glucose levels and complications of diabetes in the Pima Indians. Diabetologia 1979 Jun; 16:373-379

21. Dorf A, Ballintine EJ, Bennett PH, et al: Retinopathy in Pima Indians—Relationships to glucose level, duration of diabetes, age at diagnosis of diabetes, and age at examination in a population with a high prevalence of diabetes mellitus. Diabetes 1976 Jul; 25:554-560

22. Kamenetzky SA, Bennett PH, Dippe SE, et al: A clinical and histologic study of diabetic nephropathy in the Pima Indians. Diabetes 1974 Jan; 23:61-68

23. Jarrett RJ, Keen H: Hyperglycemia and diabetes mellitus. Lancet 1978; 2:1009-1012

24. O'Sullivan JB, Mahan CM: Evaluation of age-adjusted criteria for potential diabetes. Diabetes 1971; 20:811-815

25. Remein QR, Wilkerson HLC: The efficiency of screening for diabetes. J Chron Dis 1961; 13:6-21

26. Fajans SS, Conn JS: The early recognition of diabetes mellitus. Ann NY Acad Sci 1959; 82:208-218

27. Medical & Scientific Section British Diabetic Association: Diagnostic classification of diabetes. Br Med J 1964; 1:1568

28. World Health Organization: Technical Report Series. 1965; 310:12

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Hodgkin's Disease in a Community Oncology Center: Ten Years' Experience

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A total of 77 cases of Hodgkin's disease have been evaluated and the patients treated at our institution during the past ten years. Advances in diagnostic technology and therapy have improved the outcome of the disease and overall survival. Therapy during this period has not been standardized. Radiation therapy was the primary initial treatment for stages I, II and III, with combined-modality therapy or chemotherapy alone used for more advanced stages. Five-year disease-free and overall survival for stage IA is 81 percent and 95 percent, respectively; 74 percent and 78 percent for stage IIA; 70 percent in both instances for stage IIB; 54 percent and 100 percent for stage IIIA; 75 percent and 100 percent for stage IIIB, and 57 percent and 69 percent for stage IV. Of 13 patients initially treated with chemotherapy, 77 percent have had a complete response. Of the 16 patients (88 percent) having a relapse, 14 have been salvaged with a variety of therapeutic approaches. Overall, five-year survival for 77 patients is 86 percent, with 70 percent having no relapse.

THE CARE OF PATIENTS with Hodgkin's disease has changed dramatically in the past 15 years. New approaches to staging and therapy have resulted in significantly improved survival in patients with this disease.[1-3] The purpose of this report is to decribe the results of incorporation of these advances at a nonuniversity community oncology center. We review ten years of experience with Hodgkin's disease in a community of 100,000 population, which serves a referral area of approximately 300,000.

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This report includes only patients whose initial diagnostic workup and therapy were done at this institution.

Patients and Methods

Between January 1, 1970, and September 30, 1979, a total of 77 patients with Hodgkin's disease received initial diagnostic workup and treatment at our institution. They ranged in age from 6 to 84 years (median 29 years) at the time of diagnosis. Follow-up ranged from 1 to 10 years with a mean and median of 3.8 and 3.3 years, respectively.

Diagnostic evaluation of all cases included a history and physical examination, complete blood

ABBREVIATIONS USED IN TEXT

CRX = combination chemotherapy
CT = computerized tomography
MOPP = mechlorethamine, vincristine (Oncovin), procarbazine and prednisone
TLI = total lymphoid irradiation
XRT = radiation therapy

count, serum chemistry determination and x-ray studies of the chest. Lymphography was considered a routine staging procedure during the entire period of this study, but was not done in all patients. Staging occasionally could be accurately assessed without lymphography, though patient refusal or medical contraindications accounted for some exclusions. Bone marrow biopsies were done on most patients beginning in 1972. Computerized tomography (CT) scanning has been used occasionally since 1979 to supplement other staging procedures. Laparotomy was not uniformly considered to be part of initial staging until 1972. All biopsy material was classified according to the Rye, New York criteria.[4] The Ann Arbor staging classification was uniformly applied.[5]

Therapy during this ten-year period was not standardized. Before 1977, irradiation therapy (XRT) was delivered via a cobalt teletherapy unit; an 18-MEV linear accelerator has been used since 1977. Total lymphoid irradiation (TLI) was not considered for any treatment group until 1973; before that time only involved or extended fields were treated. Treatment doses ranged from 3,500 to 4,000 rads delivered in four weeks for each field with a boost to 4,500 rads for involved areas.[6] Cyclophosphamide, vinblastine sulfate and prednisone served as primary chemotherapy for the early years of this study. Mechlorethamine hydrochloride (nitrogen mustard), vincristine sulfate (Oncovin), procarbazine hydrochloride and prednisone (MOPP)[7] constitute the most frequently administered chemotherapy regimen since 1972.

Stages I and IIA were treated with involved-field, extended-field and total lymphoid irradia-

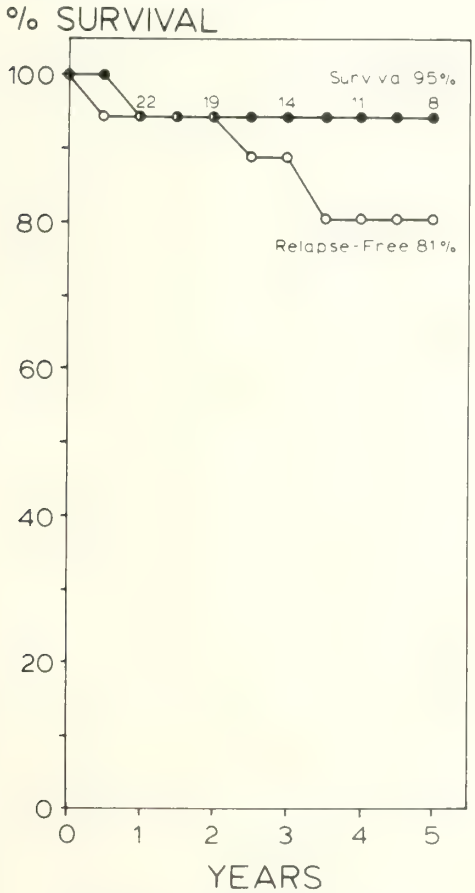

Figure 1.—Relapse-free and actuarial survivals for stage IA Hodgkin's disease.

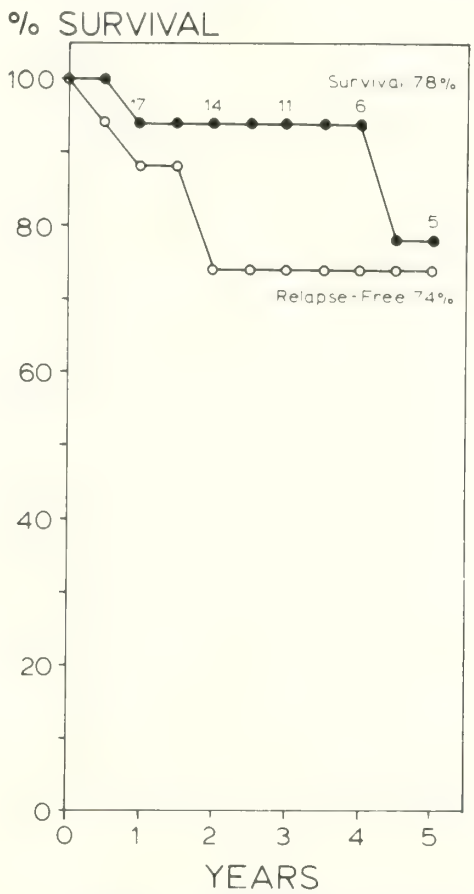

Figure 2.—Relapse-free and actuarial survivals for stage IIA Hodgkin's disease.

tion. MOPP was administered in stage IIB cases in conjunction with involved or extended fields or total lymphoid irradiation. Patients with stage IIIA were treated by total lymphoid irradiation, combination chemotherapy (CRX) or both. Patients with stages IIIB and IV received either combined modality therapy or chemotherapy alone. Incidences of relapse were usually salvaged with MOPP, though TLI and other drug combinations[8] were also used. Relapse-free and overall survival were calculated by the actuarial method.[9]

Our institution has physicians who have specialized in both radiation and medical oncology. Surgical workup of our patients has been provided by a variety of surgeons in our community.

Results

Among 23 stage IA patients, 14 received involved-field irradiation, 8 received extended-field and 1 patient was treated with TLI. Disease-free and overall survivals for stage IA disease are shown in Figure 1. Relapse-free survival at five years for stage IA is 81 percent. Overall survival is 95 percent. Relapse occurred in three patients. The first patient was staged before 1972 without laparotomy and relapse occurred in a nontreated area in the abdomen. This patient subsequently recovered following MOPP chemotherapy, remaining free of disease at five years. Overall survival rate was reduced by the death of an 84-year-old patient who received palliative irradiation only. A third patient, staged at laparotomy, had recurrence in an area outside of extended-field irradiation and has since responded to chemotherapy.

No patients with stage IB disease were seen during this ten-year period.

Stage IIA disease was found in 17 of the patients treated. Four stage IIA patients received involved-field irradiation, eight received extended-field and five received TLI. Results of therapy in 17 patients with stage IIA disease are shown in Figure 2, with a disease-free survival of 74 percent and overall survival of 78 percent. Four patients have had a relapse. Two cases of relapse,

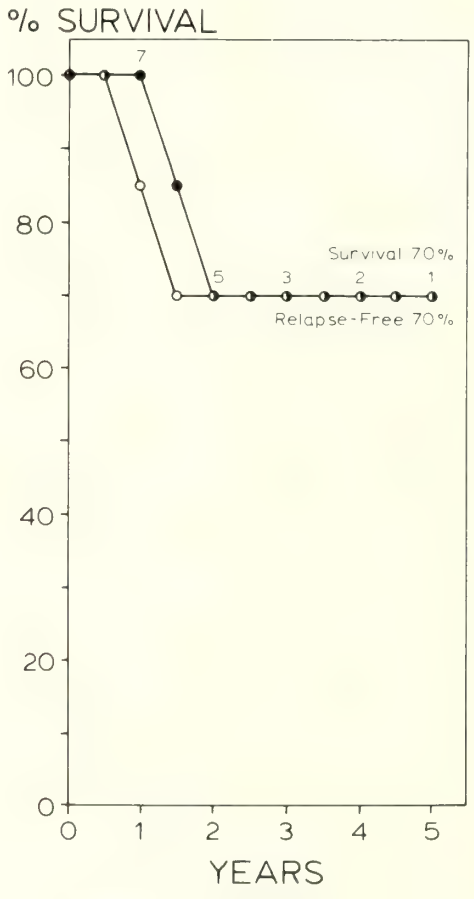

Figure 3.—Relapse-free and actuarial survivals for stage IIB Hodgkin's disease.

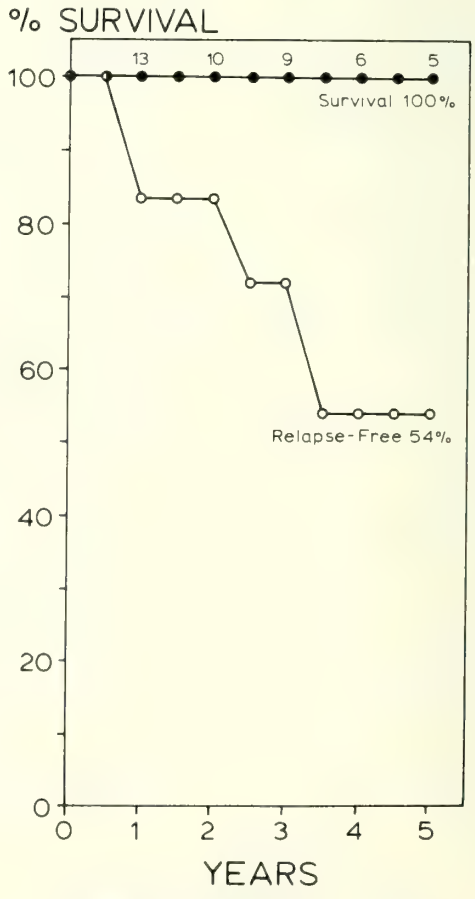

Figure 4.—Relapse-free and actuarial survivals for stage IIIA Hodgkin's disease.

both outside the treated areas, have occurred in patients seen before 1972 and staged without laparotomy. One case was salvaged with MOPP chemotherapy and the patient remains disease free at seven years. The other patient died of Hodgkin's disease after combination chemotherapy. A third patient had disease at 70 years of age, was staged without laparotomy and died of Hodgkin's disease after relapse occurred outside the treated fields. Therapy with CRX was not successful. A fourth patient, staged with laparotomy and treated with extended-field irradiation, had recurrence of disease in the liver and has persistent disease despite therapy with multiple drug combinations.

Seven patients with stage IIB disease have been treated. Relapse-free and overall survival for stage IIB were 70 percent and 70 percent respectively (Figure 3). Five stage IIB patients received involved- or extended-field XRT plus combination chemotherapy. One received TLI plus chemotherapy and one received chemotherapy only. Relapses occurred in a 76-year-old patient initially treated with MOPP only and a 9-year-old patient who received both radiation therapy and chemotherapy. Recovery in the elderly patient was possible with radiation therapy and in the younger patient with chemotherapy. However, both patients died of infection within a year of recovery, without evidence of Hodgkin's disease.

Eight of 13 stage IIIA patients received TLI, two receiving chemotherapy with MOPP only and three receiving combination chemotherapy and irradiation. Figure 4 reflects 54 percent relapse-free survival and 100 percent overall survival at five years. Three of the four relapses occurred in patients staged with a laparotomy and treated with TLI only. All three recovered with MOPP chemotherapy and remain disease free at 12, 16 and 60 months of follow-up. The fourth patient was initially diagnosed as stage III non-Hodgkin's lymphoma and treated initially with cyclophosphamide, vincristine, prednisone and bleomycin sulfate. An abdominal relapse was evaluated by laparotomy,

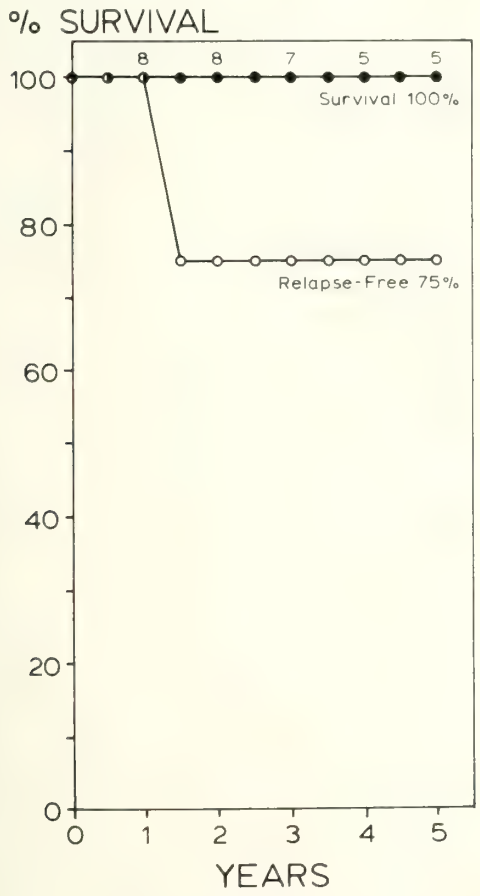

Figure 5.—Relapse-free and actuarial survivals for stage IIIB Hodgkin's disease.

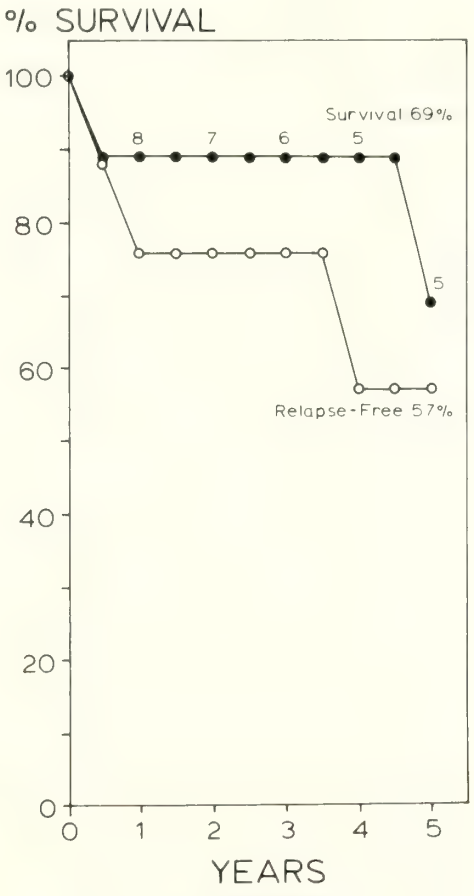

Figure 6.—Relapse-free and actuarial survivals for stage IV Hodgkin's disease.

which led to a diagnosis of mixed-cellularity Hodgkin's disease. The patient recovered with XRT and remains free of disease at 48 months.

Eight patients with stage IIIB disease were treated with various regimens. Two received extended-field irradiation therapy plus MOPP, two received TLI plus MOPP and four patients received MOPP only. Five-year survival (Figure 5) shows 75 percent disease-free survival and 100 percent overall survival. Relapse developed in two patients, one treated initially with combination chemotherapy and extended-field irradiation and salvaged with additional irradiation and combination chemotherapy; the second was treated initially with MOPP and salvaged with doxorubicin hydrochloride (Adriamycin), vinblastine, dacarbazine (DTIC-Dome) and prednisone.

Nine stage IV patients were treated, seven with CRX only (MOPP). One patient received extended-field XRT plus MOPP and one received TLI plus MOPP. Relapse-free survival at five years was 57 percent, with 69 percent overall (Figure 6). One patient presenting with bone marrow involvement had only a brief partial response to CRX and died of Hodgkin's disease after three courses of MOPP. Relapse occurred in two patients, one treated initially with both extended-field XRT and MOPP and salvaged with further XRT and CRX. The second patient was initially treated with MOPP. Recovery in this patient occurred with additional XRT and CRX. However, the patient died of acute myeloblastic leukemia five years after initial diagnosis and therapy for Hodgkin's disease.

Complications of Evaluation and Therapy

No complications or delay in therapy occurred in 43 patients staged with laparotomy. A pneumothorax developed in one patient after mediastinoscopy and mantle irradiation. Splenectomy and chemotherapy contributed to the death of a 9-year-old boy who died of meningococcemia while receiving chemotherapy for recurrence of stage IIB disease. Two cases of radiation pneumonitis cleared with corticosteroid therapy. Two cases of pericarditis resolved without specific therapy. Hypothyroidism has developed in two patients treated with radiation therapy. Herpes zoster occurred in seven patients, five of whom were treated primarily with chemotherapy. Two young women desirous of pregnancy have been unable to conceive, one 17 months after TLI and one 74 months after combined modality therapy. Two young men remain azoospermic three years after MOPP combined chemotherapy for stages II and IIIB disease. Acute leukemia developed in a 62-year-old man who had stage IV disease and five years after he received both XRT and CRX. Hodgkin's disease was not present at autopsy.

Discussion

Our ten-year experience with Hodgkin's disease reflects both the progress and the problems reported in larger clinical trials designed for the treatment and evaluation of this disease.[10-12] Relapse within irradiation fields has been a very minor problem, occurring in only one patient. Before the frequent use of staging laparotomy, relapse in lymph node areas outside of irradiation fields was a much more common problem.

A number of previously reported series have excluded patients older than 65.[1,13,14] Three of five patients over 65 years old in our series have relapsed and two have died of progressive disease. Resolution of disease was possible in the third patient with both irradiation and chemotherapy.

Thirteen previously untreated patients received MOPP as initial treatment. Nine patients (69 percent) had a complete response. All patients without B symptoms had a complete response, while only four of eight patients with B symptoms had a complete response. With a 47-month median follow-up, two patients with a complete response have relapsed, one patient without B symptoms at 8 months and one patient with B symptoms at 15 months. Both patients have had resolution of disease with TLI and CRX, respectively.

Nine patients have received CRX as therapy after relapse. MOPP has been the most frequently used drug combination, though other combinations, including doxorubicin, vinblastine, dacarbazine and prednisone have also been used. Seven of nine patients have had a complete response (78 percent). In these patients primary therapy, usually XRT, has not seriously compromised our ability to achieve effective resolution. This observation has not been uniformly supported.[15]

Seven additional patients recovered with XRT alone or XRT plus CRX. Four patients experiencing recurrent disease resistant to CRX were salvaged using XRT only. Three additional patients received combined XRT and CRX. All seven patients achieved a complete response. With a median follow-up of 54 months, two of this group of patients have had relapse. One died of Hodgkin's disease and the second patient responded to further CRX.

Overall, 16 patients in our group of 77 patients have relapsed and a variety of therapeutic regimens have produced a complete response in 14 (88 percent). Salvage failure in two patients related to resistant disease rather than failure to deliver adequate therapy.

Seven of our 77 patients have died, four of progressive Hodgkin's disease and three of complications possibly related to treatment or diagnostic workup. Two of the patients dying of disease progression were over 65 years old at the time of diagnosis.

Overall survival for our group of 77 patients is 86 percent; 70 percent are free of relapse at five years.

In the foregoing, we report both overall and relapse-free survival rates very similar to those reported from major university and research centers. We conclude that progress in the understanding and treatment of Hodgkin's disease in the past two decades has been monumental. Adequate therapy for relapsing patients and care of elderly patients are significant residual problems.

REFERENCES

1. Aisenberg AC, Qazi R: Improved survival in Hodgkin's disease. Cancer 1976; 37:2423-2429

2. Devita VT, Lewis BJ, Rozencweig M, et al: The chemotherapy of Hodgkin's disease. Cancer 1978; 42:979-990

3. Kaplan HS: Hodgkin's Disease, 2nd Ed. Cambridge, Harvard University Press, 1980

4. Lukes RJ, Carver LF, Hall TC, et al: Report of the Nomenclature Committee. Cancer Res 1966; 26:1311

5. Carbone PP, Kaplan HS, Musshoff K, et al: Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971; 31:1860-1861

6. Hellman S, Mauch P, Goodman RL, et al: The place of radiation therapy in the treatment of Hodgkin's disease. Cancer 1978; 42:971-978

7. Devita VT, Serpick A, Carbone PP: Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann Intern Med 1970; 73:881-895

8. Bonadonna G, Zucali R, Monfardini S, et al: Combination chemotherapy of Hodgkin's disease with Adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer 1975; 36:252-259

9. American Joint Committee for Cancer Staging and End-Results Reporting: Manual for Staging of Cancer 1978. Chicago, Whiting Press, 1978

10. Aisenberg AC: The staging and treatment of Hodgkin's disease. N Engl J Med 1978; 299:1228-1232

11. Rosenberg SA: The management of Hodgkin's disease. N Engl J Med 1978; 299:1246-1247

12. Rosenberg SA, Kaplan HS, Glatstein EJ, et al: Combined modality therapy for Hodgkin's disease. Cancer 1978; 42:991-1000

13. Goodman R, Mauch P, Piro A, et al: Stages IIB and IIIB Hodgkin's disease: Results of combined modality treatment. Cancer 1977; 40:84-89

14. Hoppe RT: Radiation therapy in the treatment of Hodgkin's disease. Semin Oncol 1980; 7:144-154

15. Weller SA, Glatstein EJ, Kaplan HS, et al: Initial relapses in previously treated Hodgkin's disease. Cancer 1976; 37:2840-2846

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Medical Progress

Hyperalimentation in Cancer

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A growing body of work has been addressed to the hypothesis that because patients with cancer who have poor nutritional status have a worse prognosis, increased nutritional support in these patients will result in better tolerance of surgical interventions, chemotherapy and radiation therapy, and a better outcome from the cancer. Although the hypothesis is an attractive one, there is only a single well-conducted, randomized, prospective trial to date that shows that active nutritional support is of benefit in the therapy of patients with cancer. Based on this review of the literature, it is felt that though cachexia is clearly of negative import in patients with cancer, there is little evidence to support the hypotheses that any nutritional support changes the outcome or the course of therapy of patients with cancer. It seems reasonable to continue the nutritional support to cachectic patients with cancer concomitant with specific anticancer therapy, but supportive nutritional therapy alone with postponement of specific anticancer treatment, as in awaiting weight gain or anabolism, cannot be justified with the current state of the art.

MOST PATIENTS with cancer lose weight during the course of their disease and most will also have anorexia. It has long been felt, but only recently clearly established, that this weight loss is an important prognostic determinant of morbidity and mortality.[1-6] Determined efforts have been made during the past decade to treat this cachexia so as to transfer patients from one clinical subset of cancer-bearers to another with a better prognosis based on measurements of nutritional status.[7] Many authors claim that good nutrition is of benefit to cancer patients.[7-9] It has also been reported that nutritional support could make patients with cancer less susceptible to the adverse effects of various antineoplastic therapies.[10-13] Although it is not yet known why patients having cancer die when vital organs such as heart, lungs and liver are uninvolved by neoplasm, death in cancer is most commonly related to infections,[14] where the mortality can reach 65 percent.[15] In this sense improvement in a patient's immunologic defense mechanisms has been considered one of the most beneficial achievements of nutritional support.[11]

The purpose of this review is to evaluate whether the hypothesis that effective nutritional support improves the outcome of cancer treatment is in fact supported by published clinical and experimental data. This review will also deal with the question of whether hyperalimentation is most beneficial to tumor or host.

Cancer Cachexia

Cancer cachexia is not an inevitable manifestation of a tumor's systemic effect on a patient.[14]

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ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
FFA = free fatty acid

It is a descriptive concept, which includes the net effect of several metabolic and hormonal alterations, and may not be specific for a patient with neoplastic disease. It may be that cancer cachexia is indistinguishable from other clinical conditions with cachexia and that the expression "cancer cachexia" is inappropriate.[16] The features of this syndrome have been compared with physiologic reactions accompanying other clinical conditions with cachexia, such as anorexia nervosa, malnutrition, starvation, trauma and infections. However, it has also been assumed that the increased demand of growing mass in a patient (host) may induce certain hormonal and other responses accompanying those of the normal adaptation to stress.[17] As a result, various substrates and compounds are selectively taken up by the tumor, which may act as a glucose[14] or a nitrogen trap[18]; in this manner the tumor induces a depleted nutritional state in the host. Morrison[19] has pointed out that such explanations are nothing more than a complicated way of saying that something additional is growing inside the patient-host. Perhaps the most remarkable aspect of this tumor-host relationship is the inability of the host to respond to this increased energy demand with increased nutritional intake.

The significance of certain factors such as "lipolytic factors"[20,21] and "toxohormones" (which may be released by the tumor tissue)[22-24] as a cause of cancer cachexia has been evaluated in several studies. More recently others have found alterations in the normal central nervous system physiology controlling feeding that may explain anorexia of cancer.[25]

A reasonable conclusion from various hypotheses in the literature is that cancer cachexia is the net result of many different physiologic changes in the metabolic and immunologic response to the stress of unregulated tumor growth and to an often-accompanying anorexia.

The Tumor-Host Effect

Tumor tissue is derived from transformed cells from the host. There is no evidence that tumor tissue possesses unique properties compared with the untransformed host cells in terms of overall cellular metabolism. But the malignant tumor cells lack metabolic capabilities of normal cells, while retaining some properties characteristic of undeveloped fetal tissue. The enzymatic equipment in these transformed cells is most peculiar and leads to differences in cellular metabolism. One of these differences is the diminished ability of tumor cells to oxidize glucose for energy generation and the proportionally increased reliance on glycolysis.[26,27] Although both reactions produce high-energy phosphates (mainly adenosine triphosphate [ATP]), the efficiency is strikingly different. Each molecule of glucose converted to carbon dioxide in normal cellular respiration yields 38 molecules of ATP, whereas the nonoxidative glycolysis produces only two molecules of ATP. Thus the anaerobic fermentation in tumor tissue is 19 times less efficient than the oxidative glucose conversion in normal tissue. From another standpoint the high glycolytic activity in tumor tissue increases the lactic acid load on host tissue, which must be converted to glucose in the liver through a process called gluconeogenesis. Gluconeogenesis is an energy-requiring reaction that consumes six molecules of ATP for each molecule of glucose produced. Expressed in another way, a sixth of the lactate produced by the tumor has to be oxidized to yield the energy for gluconeogenesis. For the tumor-plus-host system this means that for each molecule of glucose converted to lactic acid in tumor tissue, the tumor itself gains two molecules of energy-rich ATP but consumes four molecules of host ATP, which has to be produced elsewhere. This increased turnover of energy substrates is one of the metabolic consequences of the inefficient glucose metabolism in tumor tissue. In short, an inefficient metabolism in terms of coupling of energy occurs. The clinical relevance of these biochemical alterations relates to studies on tumor-bearing animals and cancer patients that have shown increased glucose turnover and gluconeogenesis, and increased cycling of glucose carbons.[28-30] These changes in cellular metabolism may be one explanation for the increased energy expenditure in patients with cancer.[31]

The oncofetal enzyme equipment in tumor tissue makes it an efficient substrate consumer compared with nonmalignant tissue. However, the metabolic rate as such does not seem to be distinctly different from that of other rapidly renewing tissues such as mucosal cells of the gastrointestinal tract. As Costa[32] has pointed out tumor tissue rarely exceeds 2 percent to 3 percent of the body weight of a patient with cancer. With an

overall turnover rate comparable with that of normal rapidly regenerating cells, the tumor cannot be the main cause of cachexia in terms of a "nitrogen trap." It also seems likely that the "energy trap" is related more to tumor-host interaction, with inefficient energy cycling, than to an unusually high metabolic rate with increased energy demands by the tumor cells.

Part of the negative energy state in patients with cancer is associated with increased metabolic processes such as interorgan cycling of glucose carbons, gluconeogenesis, glucose turnover rate and basal metabolic rate.[29,31-35] Increased gluconeogenesis, however, is not specific for cancer disease. From a teleological viewpoint, the body's first priority in the face of the metabolic stress and trauma of an inadequate nutritional supply is to ensure an uninterrupted supply of glucose for the central nervous system and the erythrocytes. Initially, this is carried out by mobilizing glycogen stores and by gluconeogenesis from protein. Glycerol from lipolysis stimulated by norepinephrine is one of the major precursors for gluconeogenesis in cancer.[21] The increased free fatty acid (FFA) concentration decreases insulin-dependent glucose uptake. The insulin effect is also blocked by an increase in growth hormone activity. In clinical situations this pattern of metabolic reaction is seen as insulin resistance[36] as evidenced by high levels of plasma glucose after infusion of glucose solution. The gluconeogenesis from these precursors in cancer results in depleted glycogen stores and greatly reduced lipid stores.[37] Consequently, cancer patients are more vulnerable to acute stress factors such as infections and surgical trauma.

Hyperalimentation

In starved or traumatized patients, immediate nutritional support has become a routine part of treatment. This support often can be adjusted to a patient's metabolic needs in terms of severity of injury—for example, multiplicity of trauma or area of burn size. The duration of need for nutritional support often can be anticipated in an injured patient. In comparison, the point when a change to anabolism with nutritional support can occur in a patient with cancer is very uncertain. By the time a patient is seen, the degree of nutritional deficit is often already much greater. Nutritive therapy or hyperalimentation in cancer patients therefore has been established according to certain standard procedures. This nutritional support is started before specific antitumor therapy with the hope of achieving anabolism in the tumor-host as shown by weight gain and a positive nitrogen balance, which has always been considered favorable. Nonetheless, weight gain can occur without protein gain, and body weight is not a reliable guide to changes in lean body mass.[38] Many factors influence nitrogen balance; for example, bedridden patients may in fact be in a negative nitrogen state without inadequate nutritional support simply because of decrease in activity.

It has long been anticipated that energy-producing nutrients should be given in conjunction with nitrogenous compounds.[39,40] It has also been shown that glucose and amino acids spare more body protein than amino acids alone in patients with cancer who undergo surgical procedures.[41] These findings have been the basis for standard infusion regimens of solutions containing dextrose of 750 to 1,000 grams per day and amino acids at various concentrations. To these infusion solutions vitamins and electrolytes have been added according to established needs. Three fatty acids are considered essential: linolenic, linoleic and arachidonic. Deficiency of these fatty acids leads to skin and wound healing problems and difficulties in metabolizing other fatty acids, resulting in fatty infiltration of the liver.[42,43] Administration of 500 ml of Intralipid (Cutter Medical Division of Cutter Laboratories, Berkeley, CA 94710), 20 percent solution weekly, has been considered sufficient to prevent essential fatty acid deficiency.[43-46] In summary, hyperalimentation in these patients should consist of 500 to 1,000 grams of glucose daily, with the addition of amino acids such as 500 ml of a crystalline amino acid 8.5 percent solution along with electrolytes, vitamins and biweekly fat.

Typically patients receiving hyperalimentation for as few as seven days gain weight. However, it has recently been shown that this weight gain consists mainly of water and fat.[39,47,48] Patients have even been found to lose weight during intravenous administration of nutrients but to increase body-water content. Tumor-hosts have also been known to have disturbed water and electrolyte balance even during ad libitum intake.[49] It can be concluded that weight gain can occur without protein gain in patients who are being fed intravenously and that body weight is not a reliable guide to changes in lean body mass or fat.[50]

High infusion rates of glucose increase the

metabolic rate and carbon dioxide (CO_2) production, which results in self-defeating hypermetabolism.[51-53] It may be that infusion rates of glucose in excess of 5 mg per kg of body weight per minute increase metabolism and lipogenesis. It has also been suggested that a maximum of 60 percent of infused glucose is directly oxidized for energy and that this proportion falls with increasing infusion rates; any additional glucose is converted to fat. Large infusions of glucose may increase the ventilatory load by increasing CO_2 production and water retention. This critical load of 5 mg a minute is exceeded with 500 grams of glucose to a 59-kg (130-pound) patient during 24 hours. However, the studies referred to above are flawed, fail to account for internal cycling and are not universally accepted.

Lipids have been used routinely as calorie sources for many years in certain countries. The rationale for this use involves the ability to deliver a high ratio of calories per volume of infusion solution through peripheral veins, the avoidance of increased fatty liver development caused by high glucose loads and the provision of essential fatty acids. It has recently been shown that the glucose-fatty acid cycle is of questionable physiologic significance in terms of regulating basal glucose and FFA concentrations. Infusing lipids simultaneously with glucose does not decrease the efficiency with which the infused glucose is metabolized.[53] Also, at high infusion rates of glucose, as much as 30 percent of the energy supply is wasted on lipogenesis.[52] The differential effect of various substrates on tumor growth has long been established. However, only recently was a clear-cut beneficial effect of high lipid infusion ratio shown on host tissue maintenance versus tumor growth in tumor-bearing rats.[54] If this effect can be confirmed in cancer patients, it certainly would influence the current policy of providing lipids as a calorie source in oncologic hyperalimentation.

Therapeutic Effects of Nutritional Support

It is interesting to note that high-glucose load regimens have been used in the treatment of hundreds of patients over the years without overt complications. This treatment also has induced striking changes in immunocompetence[9,11] in patients and in experimental tumor-host systems,[55] which has been a criterion for its beneficial effects. The overall favorable outcome, however, of specific antitumor therapy in hyperalimented patients in a controlled, prospective randomized study has been shown in only one study.

In one randomized, controlled, clinical trial of preoperative intravenous nutritional support of patients with stomach or esophageal cancer, a significant effect was found on rates of wound sepsis only. The main conclusion from this study was that although such clinical trials are extremely hard to complete, there seems to be a subset of patients with cancer who benefit more than others from nutritional support.[56] One measurement used to identify this subgroup was the serum albumin concentration.[57] Although isolated laboratory values have have been shown to be useful, the evaluation of the overall effect of nutritional support of hyperalimentation preferably should involve a significant change in the outcome by all types of treatment for the specific tumor in a prospective randomized trial. The number of studies are limited,[10,48,56,58-66a] but a few well-organized retrospective clinical studies do exist, in addition to data gathered from studies on tumor-bearing animals. It is fair to say that there is only one properly conducted randomized prospective trial that shows a statistically significant beneficial effect in tumor patients treated with nutritional support.

A randomized prospective trial has shown that patients undergoing major upper gastrointestinal tract surgical procedures have a lower mortality when preoperative and postoperative hyperalimentation is given as compared with standard therapy. There was no beneficial effect on major complications possibly related to malnutrition, such as wound and anastomotic disruption and sepsis.[66b] Interestingly, this beneficial effect was seen in all patients and not merely in malnourished patients. This study, then, does not totally support the concept that *malnourished* patients are improved by perioperative parenteral nutrition, but argues that all patients with major operations for cancer should be supported by parenteral nutrition.

Several authors have proposed that the conversion of lactate to glucose via the Cori cycle could result in an important energy drain and, as pointed out earlier, could result in futile cycling of glucose and thus contribute to the cachexia of cancer.[14,30,33,67] As the host-organ tissue cells harbor the ability to adapt to low-glucose states that the tumor does not possess, blocking this gluconeogenesis would seem rational antitumor therapy. There are several compounds reported capable of reducing or blocking gluconeogenesis.[68-71] Some

of these inhibitors have been reported to be capable of inhibiting in vivo growth of experimental tumors.[35] It is interesting to note that the host animals in this study by Gold at the same time decreased their total body weight. Unfortunately, completed clinical trials of one of the blocking agents, hydrazine sulfate, have failed to show either direct antitumor effect or nutritional benefits for patients with cancer.[34] A physiologic block of gluconeogenesis might be realized from adequate nutritional support that would suppress gluconeogenesis from amino acids. However, this effect is accompanied by increased glucose cycling,[72] which minimizes any beneficial effect.

In starvation or semistarvation, which in some respects resembles anorexia of cancer, gluconeogenesis is not increased to the same extent as in acute metabolic situations. The central nervous system switches from glucose to the use of ketone bodies as the main energy source. Lipolysis increases with increased free fatty acid content and transport to the liver for oxidation to ketone bodies. However, starvation is a *hypometabolic* state with a reduction in turnover of nutrients and with ketone bodies playing a regulatory role,[73,74] and cancer is a *hypermetabolic* state with increased metabolic turnover. Moreover, ketosis is an uncommon phenomenon in cancer patients and in tumor-bearing animals. In starvation there seem to be reduced cell growth rates. This could possibly be a reaction induced by ketosis.[75] Ketone bodies have also been shown to reduce the growth of malignant cells in growth culture. It therefore has been speculated that induced ketosis in cancer patients by infusion of lipid solutions might be of therapeutic benefit. No controlled data have shown that this is the case, though lipids as energy substrate have been shown to have host-tissue maintenance properties.[54]

Tumor tissue is dependent solely on glucose for its energy production, which is necessary for cell growth and replication. When the availability of glucose is limited, tumor tissue competes successfully with host tissue for glucose substrates via gluconeogenesis not only from tumor-produced lactic acid but also from other sources such as amino acids derived from skeletal muscle. Because of this competition, it would seem difficult on theoretic grounds to starve the tumor by feeding the tumor-bearing host energy-rich nutrients other than glucose (such as fat). There are experimental data indicating that specific substrate compositions may promote host maintenance equivalent to carbohydrate-based nutritional support with significantly less stimulation of tumor growth.[54]

The incomplete metabolic features in tumor tissue also seem to make it susceptible to other forms of substrate differentiation. In vitro studies have shown that methionine deprivation inhibits tumor cell growth from some specific lines without affecting normal cells.[76] This has not yet been confirmed in vivo.

In summary, these is only one beneficial result from prospective randomized studies that have been published. Some of the studies have shown improvement of isolated physiologic measurements such as a decreased rate of wound infections[56] and less of a drop in granulocyte count[62] and leukocyte count[10] in combination with chemotherapy. Only one study has been able to show significantly increased survival.[66b]

Nutrition and Chemotherapy

There has always been a suspicion that tumor tissue would gain more from nutritional support than patient-host tissue. The rationale for this theory is that a growing tissue has a high affinity for substrates and that tumor growth in some instances may be retarded by anorexia of the host and concomitant nutritional shortage. In tumor-bearing animal systems this has been shown to be true, at least during a short period.[77,78] It was also shown that parenteral hyperalimentation induced higher mitotic activity in tumor tissue cells, which indicated that intravenous feeding caused the tumor to undergo faster cellular turnover.[77]

Chemotherapy acts at the cellular level to destroy tumor cells or to prevent their replication. Different antineoplastic drugs act during different phases of the cell cycle. G_1 is the first growth period in which enzymes, structural proteins and organelles are synthesized. During S phase DNA synthesis occurs. G_2 is the second growth phase and in M phase mitosis and cell division occur. Vinblastine and vincristine sulfate are examples of drugs that interfere with mitosis and thus block cell division, whereas 5-fluorouracil interferes with thymidine synthetase resulting in a blockage of DNA synthesis. Cell-cycle-specific drugs act best during proliferation phases and much effort has gone toward planning chemotherapy schedules according to these principles of timing. It has been suggested that nutritional support could stimulate replication of cancer cells, making cell-cycle-specific drugs more effective in treatment. As an

example, methotrexate, a chemotherapeutic agent that inhibits DNA synthesis, was shown to be more effective in a group of rats in which tumor growth rate was increased by nutritional manipulation.[79]

As in all instances in which conclusions are drawn from experimental tumor systems, the ratio of tumor mass to host and the time for tumor development, which may differ in relation to cancer in humans, must be taken into account. For example, if 10 to 20 days of nutritional manipulation seem to change the growth rate of sarcoma in rats, this may be comparable with months of nutritional repletion in patients with cancer. In this context the few proved effects of short-term nutritional support in cancer patients during specific anticancer treatment involve the maintenance of rapidly renewable and vulnerable tissues such as leukocytes and cells of the gastrointestinal mucosa.

Starvation is known to reduce rat liver DNA synthesis.[80] Such a decrease should theoretically decrease a host's susceptibility to the adverse effects of, for example, 5-fluorouracil. When the tumor grows autonomously with priority over the host in situations with limited nutritional supply, its growth is less affected by starvation.[81] Such a theory could argue against the beneficial effects of nutritional support during chemotherapy.[82]

Conclusion

It is necessary to remember that cancer cachexia is the result not only of semistarvation but of a complex metabolic reaction. In tumor-bearing hosts and patients with cancer there are abnormalities in metabolism of energy, carbohydrates, lipids and protein. There are numerous alterations in the activity of host tissue enzymes and changes in endocrine homeostasis and immune mechanisms.[83] Only the complete definitive treatment of the underlying malignant lesion can reverse the cachectic syndrome. From available data it is clear that there are a variety of tumors that affect their hosts differently. So far no conclusive data exist about the type or types of substances or other mechanisms by which the tumor may induce the cachexia syndrome.

The causes of malnutrition in cancer patients can be summarized as follows: anorexia, increased basal metabolic rate or hypermetabolism in the host, the nutritional demands of the tumor and effects of oncologic therapy.[84] All these factors lead to cachexia, which has been a challenge for nutritional therapy. Such treatment has been reported of value in certain subgroups of patients with cancer in terms of improvement in the immune status and rate of wound healing.[1,2,9,11,56] However, these patients also appear to respond better to specific antitumor therapy; the nutritional reaction to hyperalimentation thus could be regarded as a prognostic factor. In this regard the hyperalimentation as such is of minor importance as an antitumor treatment regimen.[12,60,85]

The finding that hyperalimentation mainly leads to accumulation of adipose tissue has been regarded as an indication of a block in repletion of lean body mass in cancer patients.[86] However, the same reaction is also seen in patients without cancer, indicating that this may be a general reaction to short-term energy loads in states of disturbed metabolism of any cause.[38,47]

The evidence that nutritional support of patients with cancer is of any benefit in increasing survival or causing significant changes in metabolic values associated with higher response rates to various forms of specific antineoplastic therapy is marginal at best.[48,61,63,85-87] There is also no clear-cut evidence of significantly accelerated tumor growth rate under the influence of clinical hyperalimentation.[55,72,88-90] As several reports have been able to show, nutritional therapy may not significantly prolong life but it can improve the quality of life,[31] in part by improving a patient's ability to tolerate the side effects of various forms of treatment.[1,9-13,56] It seems reasonable, therefore, to continue the nutritional support to cachectic cancer patients concomitant with specific anticancer therapy. Supportive nutritional therapy alone, however, or postponing specific anticancer treatment (awaiting weight gain or anabolism) cannot, with today's knowledge, be justified.

REFERENCES

1. Small BF, Mullen JL, Buzby GP, et al: The efficacy of nutritional assessment and support in cancer surgery. Cancer 1981; 47: 2375-2381

2. Frankman C, Freeman M, Beck J, et al: Prognostic significance of pretreatment nutritional parameters in patients with lung cancer receiving chemotherapy and intravenous hyperalimentation (IVH). Proc Am Assoc Cancer Res 1980; 21:183

3. Dindogru A, Bera MD, Rutkowski Z, et al: Selection of cancer patients for total parenteral nutrition. Proc Am Assoc Cancer Res 1980; 21:377

4. Holter AR, Fischer JE: The effects of perioperative hyperalimentation on complications in patients with carcinoma and weight loss. J Surg Res 1977 Jul; 23:31-34

5. Issell BF, Frankman C, Beck J, et al: Nutritional parameters as prognostic factors in lung cancer patients. Proc Am Assoc Cancer Res 1979; 20:203

6. Nixon D, Rudman D, Heymsfield S, et al: Protein calorie undernutrition: Prevalence and relation to survival. Proc Am Assoc Cancer Res 1979; 20:433

7. Drasin H, Rosenbaum EH, Stitt CA, et al: The challenge of nutritional maintenance in cancer patients. West J Med 1979 Feb; 130:145-152

8. DeWys WD, Kisner D: Maintaining caloric needs in the cancer patient. Contemp Surg 1979; 15:25-32

9. Copeland EM, Daly JM, Ota DM, et al: Nutrition, cancer,

and intravenous hyperalimentation. Cancer 1979 May; 43(Suppl): 2108-2116

10. Clamon G, DeWys W, Kubota T, et al: Hyperalimentation as an adjunct to therapy for small cell lung cancer: Preliminary report on safety and nutritional efficacy. Proc Am Assoc Cancer Res 1981; 21:421

11. Copeland EM, Daly JM, Dudrick SJ: Nutrition as an adjunct to cancer treatment in the adult. Cancer Res 1977 Jul; 37: 2451-2456

12. Jordan WM, Valdivieso M, Freeman M, et al: Importance of nutritional assessment and pre-chemotherapy hyperalimentation in adenocarcinoma of the lung. Proc Am Assoc Cancer Res 1976; 20:412

13. Serrou B, Joyeux H, Dubois JB, et al: Pilot study of peripheral intravenous nutrition in patients bearing solid tumors—A simple and valuable adjunct to chemotherapy. Proc Am Assoc Cancer Res 1979; 20:305

14. Shapot VS: On the multiform relationship between the tumor and the host. Adv Cancer Res 1979; 30:89-150 (210 ref)

15. Sickles EA, Young VM, Greene WH, et al: Pneumonia in acute leukemia. Ann Intern Med 1973 Oct; 79:528-534

16. Sudjian AV: A hypothesis—Cancer cachexia or cachexia in cancer? Acta Chir Scand Suppl 1980; 498:155-159

17. Van Eys J: The metabolic consequences of cancer, *In* Wollard JE (Ed): Nutritional Management of the Cancer Patient. New York, Raven Press, 1979

18. Mider GB: Some aspects of nitrogen and energy metabolism in cancerous subject—A review. Cancer Res 1951; 11:821-829

19. Morrison SD: Control of food intake in cancer cachexia: A challenge and a tool. Physiol Behav 1976 Oct; 17:705-714 (150 ref)

20. Costa G, Holland JF: Effects of Krebs-2 carcinoma on the lipid metabolism of male Swiss mice. Cancer Res 1962; 22:1081-1083

21. Kralovic RC, Zepp FA, Cenedella RJ: Studies of the mechanism of carcass fat depletion in experimental cancer. Eur J Cancer 1977 Oct; 13:1071-1079

22. Suda M, Tanaka T, Sue F, et al: Dedifferentiation of sugar metabolism in the liver of tumor-bearing rats. Gan 1966; 1:127-141

23. Suda M, Tanaka T, Yanagi S, et al: Dedifferentiation of enzymes in the liver of tumor-bearing animals. Gan 1972; 13:79-93

24. Watanabe M: Immunosuppression induced by "toxohormone" from mouse tumor cells in culture. Tohoku J Exp Med 1979 Jul; 128:233-239

25. Krause R, James JH, Ziparo V, et al: Brain tryptophan and the neoplastic anorexia-cachexia syndrome. Cancer 1979 Oct; 44: 1003-1008

26. Ichihara A: Relation of the characteristics of liver cells during culture, differentiation and carcinogenesis, *In* Criss WE, Ono T, Sabine JR (Eds): Control Mechanisms in Cancer. New York, Raven Press, 1976

27. Aisenberg AC: Glycolysis and Respiration of Tumors. New York, Academic Press, 1960

28. Holroyde CP, Axelrod RS, Skutches CL, et al: Lactate metabolism in patients with metastatic colorectal cancer. Cancer Res 1979 Dec; 39:4900-4904

29. Waterhouse C: How tumors affect host metabolism. Ann NY Acad Sci 1974; 230:86-93

30. Waterhouse C, Jeanpretre N, Keilson J: Gluconeogenesis from alanine in patients with progressive malignant disease. Cancer Res 1979 Jun; 39(6 Pt 1): 1968-1972

31. Warnold J, Lundholm K, Scherstén T: Energy balance and body composition in cancer patients. Cancer Res 1978 Jun; 38: 1801-1807

32. Costa G: Cachexia, the metabolic component of neoplastic diseases. Cancer Res 1977 Jul; 37(7 Pt 2):2327-2335 (107 ref)

33. Holroyde CP, Gabuzda TG, Putman RC, et al: Altered glucose metabolism in metastatic carcinoma. Cancer Res 1975 Dec; 35:3710-3714

34. Schein PS, Kisner D, Haller D, et al: Cachexia of malignancy: Potential role of insulin in nutritional management. Cancer 1979 May; 43:2070-2076

35. Gold J: Cancer cachexia and gluconeogenesis. Ann NY Acad Sci 1974; 230:103-110

36. Lundholm K, Holm G, Scherstén T: Insulin resistance in patients with cancer. Cancer Res 1978 Dec; 38:4665-4670

37. Lundholm K, Edström S, Karlberg HI, et al: Relationship of food intake, body composition, and tumor growth to host metabolism in nongrowing mice with sarcoma. Cancer Res 1980 Jul; 40:2516-2522

38. Hill GL, Bradley JA, Smith RC, et al: Changes in body weight and body protein with intravenous nutrition. JPEN 1979 Jul-Aug; 3:215-218

39. Peters C, Fischer JE: Studies on calorie to nitrogen ratio for total parenteral nutrition. Surg Gynecol Obstet 1980 Jul; 151: 1-8

40. Long JM III, Wilmore DW, Mason AD Jr, et al: Effect of carbohydrate and fat intake on nitrogen excretion during total intravenous feeding. Ann Surg 1977 Apr; 185:417-422

41. Young GA, Hill GL: A controlled study of protein-sparing therapy after excision of the rectum: Effects of intravenous amino acids and hyperalimentation on body composition and plasma amino acids. Ann Surg 1980 Aug; 192:183-191

42. Holman RT: The ratio of trienoic:tetraenoic acids in tissue lipids as a measure of essential fatty acid requirement. J Nutr 1960; 70:405-406

43. Wretlind A: Parenteral nutrition. Surg Clin North Am 1978 Oct; 58(5):1055-1070

44. Dudrick SJ, Copeland EM: Parenteral hyperalimentation, *In* Nyhus L (Ed): Surgery Annual, Vol 5. New York, Appleton-Century-Crofts, 1973, pp 69-95

45. Goodgame JT, Lowry SF, Brennan MF: Essential fatty acid deficiency in total parenteral nutrition: Time course of development and suggestions for therapy. Surgery 1978 Aug; 84:271-277

46. Stein P, Buzby GP, Hargrove WC III, et al: Essential fatty acid deficiency in patients receiving simultaneous parenteral and oral nutrition. JPEN 1980; 4:343-345

47. Yeung CK, Smith RC, Hill GL: Effect of an elemental diet on body composition—A comparison with intravenous nutrition. Gastroenterology 1979 Oct; 77:652-657

48. Popp MB, Fischer RI, Wesley R, et al: A prospective randomized study of adjuvant parenteral nutrition in the treatment of advanced diffuse lymphoma: Influence on survival. Surgery 1981 Aug; 90:195-203

49. Morrison SD: Water intake and exchange and hydration of rats during growth of Walker 256 carcinoma. J Natl Cancer Inst 1971 Apr; 46:825-830

50. Jeejeebhoy KN: Is more better? Is weight water?—The significance of weight gain during parenteral nutrition with amino acids and dextrose. Gastroenterology 1979 Oct; 77:799-800

51. Wolfe RR, O'Donnell FT Jr, Stone MD, et al: Investigation of factors determining the optimal glucose infusion rate in total parenteral nutrition. Metabolism 1980; 29:892-900

52. Mullany CJ, Wolfe RR, Burke JF: The fate of a glucose infusion in fasting and fed guinea pigs. J Surg Res 1980; 29:116-125

53. Mullany CJ, Wolfe RR, Burke JF: Interrelationships between glucose and free fatty acid (FFA) metabolism during glucose and lipid infusions. JPEN 1981; 5:186

54. Buzby GP, Mullen JL, Stein TP, et al: Host-tumor interaction and nutrient supply. Cancer 1980 Jun 15; 45:2940-2948

55. Daly JM, Copeland EM, Dudrick SJ: Effects of intravenous nutrition on tumor growth and host immunocompetence in malnourished animals. Surgery 1978 Nov; 84:655-658

56. Heatley RV, Williams RH, Lewis MH: Pre-operative intravenous feeding—A controlled trial. Postgrad Med J 1979 Sep; 55:541-545

57. Williams RH, Heatley RV, Lewis MH: Proceedings: A randomized controlled trial of preoperative intravenous nutrition in patients with stomach cancer. Br J Surg 1976 Aug; 63:667

58. Holter AR, Rosen HM, Fischer JE: The effects of hyperalimentation on major surgery in patients with malignant disease: A prospective study. Acta Chir Scand [Suppl] 1976; (466):86-87

59. Popp MB, Kirkemo A, Morrison SO: Effects of total parenteral nutrition on tumor and body composition in the rat methylcholanthrene (MCA)-induced sarcoma model. Proc Am Assoc Cancer Res 1981; 22:57

60. Valerio D, Overett L, Malcom A, et al: Nutritional support for cancer patients receiving abdominal and pelvic radiotherapy: A randomized prospective clinical experiment of intravenous versus oral feeding. Surg Form 1978; 29:145-148

61. Lanzotti V, Copeland E, Bhuchar V, et al: A randomized trial of total parenteral nutrition (TPN) with chemotherapy for non-oat cell lung cancer. Proc Am Assoc Cancer Res 1980; 21:377

62. Issell BF, Valdivieso M, Zaren HA, et al: Protection against chemotherapy toxicity by IV hyperalimentation. Cancer Treat Rep 1978 Aug; 62:1139-1143

63. Shamburger RC, Brennan MF, Goodgame JT, et al: Effect of total parenteral nutrition on metabolic parameters of patients undergoing ablative chemotherapy. Proc Am Assoc Cancer Res 1981; 22:420

64. Popp MB, Fischer RJ, Simon RM, et al: A prospective randomized study of adjuvant parenteral nutrition in the treatment of lymphoma: I. Effect on drug tolerance. Cancer Treat Rep 1982 (In Press)

65. Valdivieso M, Bodey GP, Benjamin RS, et al: Role of intravenous hyperalimentation as an adjunct to intensive therapy for small cell bronchogenic carcinoma: Preliminary observations. Cancer Treat Rep 1982 (In Press)

66a. Nixon E, Kutner MU, Ansley J, et al: Survival with and without hyperalimentation. Cancer Treat Rep 1982 (In Press)

66b. Müller JM, Dienst C, Brenner U, et al: Preoperative parenteral feeding in patients with gastrointestinal carcinoma. Lancet 1982; 1(8263):68-72

67. Gold J: Proposed treatment of cancer by inhibition of gluconeogenesis. Oncology 1968; 22:185-207

68. DiTullio NW, Berkoff CE, Blank B, et al: 3-Mercaptopicolinic acid, an inhibitor of gluconeogenesis. Biochem J 1974 Mar; 138:387-394

69. Jomain-Baum M, Schramm VL, Hanson RW: Mechanism of 3-mercaptopicolinic acid inhibition of hepatic phosphoenolpyruvate carboxykinase (GTP). J Biol Chem 1976 Jan 10; 251:37-44

70. Toews CJ, Ruderman NB, Lowy C, et al: The mechanism of inhibition of gluconeogenesis by pent-4-enoic acid. Fed Proc 1969; 28:411

71. Ray PD, Hanson RL: Inhibition of gluconeogenesis by hydrazine. Fed Proc 1969; 28:411

72. Brennan MF: Total parenteral nutrition in the cancer patient. New Engl J Med 1981; 305:375-381

73. Freinkel N: The role of nutrition in medicine—Recent developments in fuel metabolism. JAMA 1978 May 5; 239:1868-1872

74. Garattini S, Bizzi A, Donelli MG, et al: Anorexia and cancer in animals and man. Cancer Treat Rev 1980; 7:115-140

75. Conyers RA, Need AG, Rofe AM, et al: Nutrition and cancer (Letter). Br Med J 1979 Apr; 1:1146

76. Kreis W: Effect of nutritional and enzymatic methionine deprivation upon human normal and malignant cells in tissue culture. Proc Am Assoc Cancer Res 1976; 20:113

77. Cameron IL, Pavlat WA: Stimulation of growth of a transplantable hepatoma in rats by parenteral nutrition. J Natl Cancer Inst 1976 Mar; 56:597-602

78. Popp MB, Morrison SD, Brennan MF: Total parenteral nutrition in a methylcholanthene-induced rat sarcoma model. Cancer Treat Rep 1982 (In Press)

79. Daly JM, Reynolds HM, Rowlands BJ, et al: Tumor growth in experimental animals: Nutritional manipulation and chemotherapeutic response in the rat. Ann Surg 1980 Mar; 191:316-322

80. Reilly JJ, Goodgame JT, Jones DC, et al: DNA synthesis in rat sarcoma and liver: The effect of starvation. J Surg Res 1977 Mar; 22:281-286

81. Goodgame JT Jr, Lowry SF, Reilly JJ, et al: Nutritional manipulations and tumor growth—I. The effects of starvation. Am J Clin Nutr 1979 Nov; 32:2277-2284

82. Stein TP, Hargrove WC 3rd, Miller EE, et al: Effect of nutritional status and 5 fluorouracil on protein synthesis in parenterally alimented LEW/Mai rats. J Natl Cancer Inst 1979 Aug; 63:379-382

83. Theologides A: Cancer cachexia. Cancer 1979 May; 43 (Suppl):2004-2012

84. Panel report on nutritional support of patients with cancer. Am J Clin Nutr 1981; 34:1199-1205

85. Benrubi G, Knox L, Dodd D, et al: Response to total parenteral nutrition (TPN) in disseminated gynecologic malignancies. Proc Am Assoc Cancer Res 1981; 22:433

86. Nixon DW, Rudman D, Heymsfield SB, et al: Abnormal hyperalimentation response in cachectic cancer patients. Proc Am Assoc Cancer Res 1979; 21:173

87. Serrou B, Cupissol D: Adjunct effect of parenteral nutrition depends on the tumor sensibility to chemotherapy. Proc Am Assoc Cancer Res 1980; 21:358

88. Steinberg J, Stein TP, Giandomenico E, et al: Body composition alterations: Protein depleted and repleted tumor-bearing rat. Proc Am Assoc Cancer Res 1981; 22:39

89. Goodgame JT Jr, Lowry SF, Brennan MF; Nutritional manipulations and tumor growth—II. The effects of intravenous feeding. Am J Clin Nutr 1979 Nov; 32:2285-2294

90. Daly JM, Reynolds HM, Rowlands BJ, et al: Nutritional manipulation of tumor-bearing animals: Effects on body weight, serum protein levels and tumor growth. Surg Forum 1978; 29: 143-144

Specialty Conference

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Coronary Artery Spasm

Pathophysiology, Clinical Presentations, Diagnostic Approaches and Rational Treatment

DONALD C. HARRISON, MD:* In the past decade coronary artery spasm has been increasingly appreciated as a cause of angina pectoris. The recognition of this clinical syndrome has intensified the search for specific diagnostic techniques and a rational approach to therapy based on sound physiologic understanding of coronary vascular control mechanisms. Our purpose in this conference is (1) to present our current understanding of the pathophysiologic basis for coronary artery spasm, focusing on factors that control coronary artery contraction, (2) to discuss the varied clinical presentations of coronary artery spasm in patients with normal coronary arteries and in those with fixed obstructive disease and (3) to present a rational approach to treatment of these patients, emphasizing the use of the new drugs that block calcium channels in arterial smooth muscle cells.

Historical Background

In 1959 Prinzmetal and associates[1] reported findings on a small group of patients with "variant angina" who had transient ST segment elevation during episodes of chest pain. These patients were unique in that their angina usually occurred at rest or at night in a cyclic and recurrent manner. One of these patients died and was found to have severe occlusive coronary artery disease. The authors therefore postulated that variant angina was caused by spasm superimposed on areas of severe, fixed, occlusive coronary artery disease that caused the pronounced transmural ischemia and ST segment elevation. Previous writers as far back as Osler[2] had wondered about the possible contribution to angina pectoris of changes in the diameter of coronary arteries. In 1910 Osler defined angina pectoris as a disease associated with changes in the arterial wall that were "organic or functional." Other observers, such as Wilson and Johnston,[3] noted in 1941 that "attendant myocardial ischemia is due to a change in caliber of coronary arteries affected, rather than by an increase in work of the heart." Whereas it was initially believed that coronary artery spasm was a rare, variant form of angina, the advent of coronary arteriography in the late 1960's and the ability to do continuous hemodynamic monitoring in the 1970's provided a great deal of insight into the wide spectrum of patients who may have varying degrees of coronary artery spasm contributing to their anginal syndrome.

Coronary Vascular Smooth Muscle Physiology

ROBERT GINSBURG, MD:† The human epicardial coronary artery is classified histologically as a muscular artery. It varies from 1 to 4 mm in diameter and is composed of four distinct layers: intima, internal elastic lamina, media and adventitia. The intima consists only of endothelial cells and a basal lamina. The media, or middle layer of the vascular wall, is made up of smooth muscle cells and bundles of collagenous fibrils and is separated from the intima by a distinct fenestrated internal elastic lamina. Nerves, capillaries and connective tissue comprise the outermost layer,

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ABBREVIATIONS USED IN TEXT

AV = atrioventricular
ECG = electrocardiogram
PGs = prostaglandins
PGI_2 = prostacyclin
Tx = thromboxane

the adventitia (Figure 1). Electron microscopy of the coronary artery has revealed that the smooth muscle cells of the coronary artery are connected to one another by areas called nexus or tight junctions.[4] These are areas of cell membrane apposition. They allow the smooth muscle cells of the human epicardial coronary artery to communicate with one another, sharing both biochemical and electrical signals, and thus operating as a functional unit.

The smooth muscle cells of the human coronary artery depend on extracellular calcium (Ca^{2+}) for contraction and maintenance of tone. Although many factors can regulate coronary tone, such as myocardial oxygen demand, the state of the autonomic nervous system and the level of circulating vasoactive substances, all of these events are regulated through a final common pathway. This pathway involves calcium.

In the normal resting state there is a large calcium gradient across the cell membrane: 10^{-3}M Ca^{2+} on the outside cell and 10^{-7}M Ca^{2+} on the inside. When the smooth muscle cell is excited, channels or pores located in the cell membrane open and calcium rushes into the cytoplasm of the cell. The calcium then complexes with the protein calmodulin, activates myosin kinase and the result is contraction of the cell. This "trigger" calcium enters the cell and is involved in normal as well as abnormal contraction of the smooth muscle cell. Conversely, agents that block the entry of calcium into the cell at the level of the membrane will prevent contraction.

Potential Mechanisms of Coronary Artery Spasm

The exact cause of coronary artery spasm is as yet unknown though there is active ongoing re-

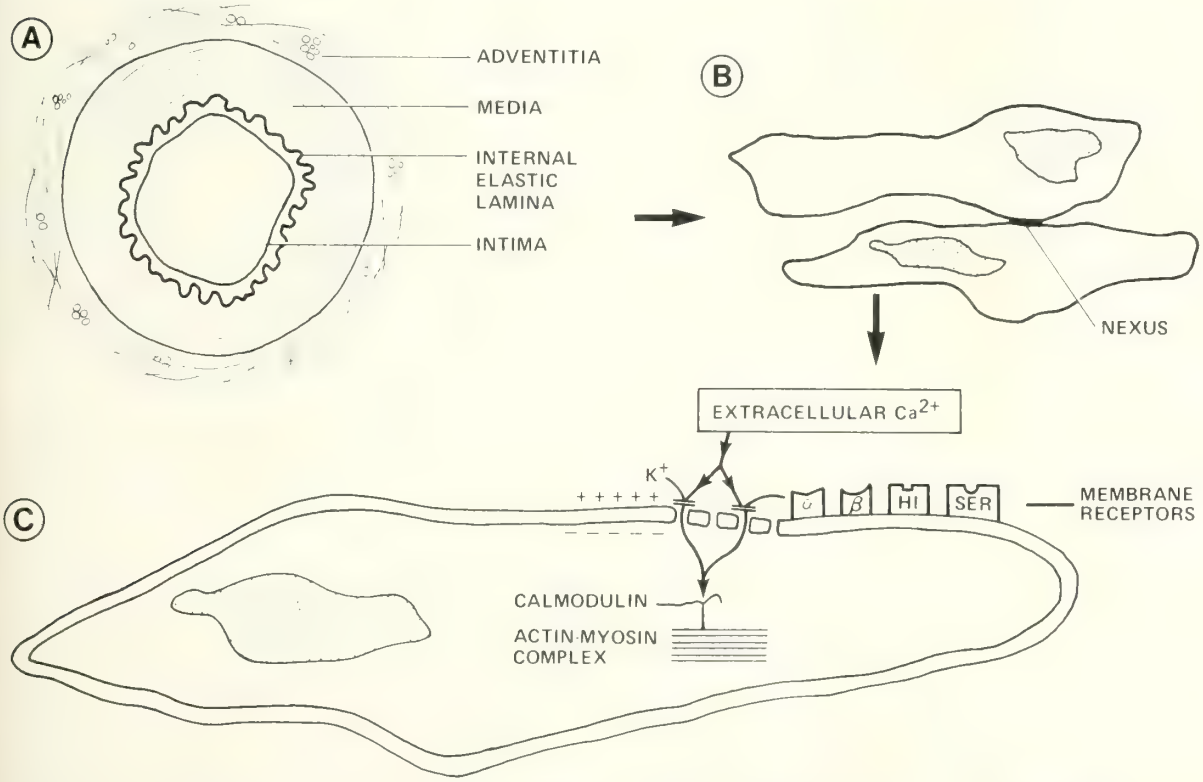

Figure 1.—A, Schematic cross-section of human epicardial coronary artery. (Reduced from magnification ×100.) **B,** Schematic of two smooth muscle cells showing nexus or gap junction—an area of cell membrane apposition. (Reduced from magnification ×4,000.) **C,** Schematic diagram of calcium (Ca^{2+}) flux through channels in membrane of single smooth muscle cell (K^+ = potassium, α = alpha, β = beta, HI = histamine, SER = serotonin). (Reduced from magnification ×40,000.)

search in this area. It is becoming clear through these intensive investigations that the normal human epicardial coronary artery is not just a passive conduit through which blood flows but is a highly reactive structure in constant motion. These vessels are subject to and under the influence of a variety of mediators, including circulating vasoactive agents and local neurogenic mechanisms. Coronary artery spasm is an exaggerated or hypercontractile response of the vessel to these various factors.

The pathophysiologic mechanisms involved in coronary spasm most likely occur at the local cellular level. Many theories have been proposed and the highlights of each will be briefly reviewed.

Neurogenic Mechanisms

Neurogenic influences, especially from sympathetic stimulation, have been implicated in spasm. It is known that α-receptor stimulation mediates vascular smooth muscle contraction and that β_2-stimulation mediates relaxation. Ricci and co-workers[5] have postulated that alterations in sympathetic activity may result in spasm. They showed that α-adrenergic blockade with intravenously administered phentolamine hydrochloride immediately reversed coronary spasm. However, both α-blockers phentolamine and phenoxybenzamine hydrochloride are also direct smooth muscle relaxants by virtue of their calcium-blocking properties; thus it is unclear through what mechanisms these blockers are operating in patients with coronary spasm.

Robertson and colleagues[6] also studied sympathetic function in their patients with coronary spasm. They found normal catecholamine and metabolite levels in these patients. At the onset and termination of spontaneous ST segment elevation they found no change in catecholamine levels. The authors concluded that there was no generalized increase in sympathetic outflow associated with initiation of attacks of coronary spasm.

The ultimate evidence for neurogenic mechanisms not being implicated in the genesis of spasm is the use of surgical denervation procedures. Bertrand and associates[7] and Clark and co-workers[8] attempted complete denervation by surgical autotransplantation of the heart. Both groups were unsuccessful in completely eliminating spasm using this method. Buda and colleagues[9] recently reported a cardiac transplant patient in whom coronary spasm developed. Electrophysiologic studies showed complete denervation, but spasm was still evident.

These studies therefore show that denervation by itself does not prevent spasm. It appears that derangement of sympathetic nervous system function is not the cause of spasm. The sympathetic system may modulate or be secondarily involved, but it is not the sole mechanism causing abnormal contraction of coronary vascular smooth muscle.

Prostaglandins

The role of prostaglandins (PGs) in causing altered vascular reactivity has undergone extensive investigation. More specifically, attention has been directed to the role of thromboxane (Tx) A_2 as a vasoconstrictor and prostacyclin (PGI_2) as a vasodilator. TxA_2 is released by aggregating platelets and can cause intense vasoconstriction. PGI_2 is produced within the vessel wall and inhibits platelet aggregation. In low concentrations PGI_2 causes relaxation of smooth muscle and in high concentrations it causes contraction of smooth muscle.

Robertson and associates[10] studied the production of TxB_2 (the hydration product of TxA_2) in patients with spasm. They conclude that TxB_2 was unlikely to cause coronary spasm, though it may be released secondarily. They, as well as A. Maseri, MD (written communication, October 1980) have also studied the effects of cyclooxygenase inhibitors, such as indomethacin and aspirin, on coronary spasm, and they have found no effect of these agents on the frequency or duration of ischemic events due to spasm. All of these studies suggest that although PGs and platelets may be involved secondarily in spasm, they are not primary medicators.

Circulating Vasoactive Amines—Local Factors

Coronary artery spasm can be provoked clinically by a wide spectrum of agents. These include ergonovine,[11] methacholine,[12] norepinephrine,[13] TRIS buffer (tromethamine)[14] and histamine.[15] Each of these agents acts pharmacologically through specific receptors found in the cell membrane of individual smooth muscle cells. This implies that the pathophysiology of coronary spasm involves a cellular mechanism beyond the level of interaction of a single agonist and its membrane receptor and that this pathway can be activated by a number of endogenous vasoactive substances. Alternatively, it is possible that areas of spasm are marked by alterations of all classes of mem-

brane receptors and that spasm may result from activation of any of them. It is hoped that future research will define the precise mechanisms, but the evidence to date suggests that coronary artery spasm is due to local abnormalities at the single cell level.

Clinical Presentation

Definition

JOHN S. SCHROEDER, MD:* Coronary artery spasm is best defined as transient, reversible focal spasm in an epicardial coronary artery resulting in myocardial ischemia, which is reversible with nitroglycerin. It is now appreciated that not only normal but severely atherosclerotic arteries are dynamic vessels that are capable of responding to a number of autonomic and humoral influences that may precipitate the transient, recurrent focal spasm leading to rest or apparent unprovoked angina pectoris.

Classical Variant Angina

Patients with typical variant angina report episodes of angina that occur predominantly at rest or while asleep. The location and distribution of the angina pectoris is typical for myocardial ischemia and is usually described as a constricting or tight, oppressive sensation in the substernal area that may radiate into the neck, jaw or inner aspect of the left arm. The pain may occur without any evident provocation or, in some patients, may also appear during emotional excitement or after cessation of exercise. The more typical presentation is pain occurring cyclically in the early morning or that awakens the patient from sleep. Pain is typically responsive to nitroglycerin taken sublingually, which results in relief in a few minutes. Pain tends to be transient in nature and may be accompanied by feelings of anxiety or shortness of breath when severe myocardial ischemia causes left ventricular dysfunction and a rise in pulmonary venous pressures. A patient tends to have a similar pain pattern on a daily basis, though the frequency of pain can be highly variable, occurring frequently for a few days and then disappearing for a few days to several months.[16] This cyclic occurrence is important when considering provocative testing because when patients are in an active phase small amounts of ergonovine maleate may produce intense spasm.

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In patients with spasm there may be a history of migraine headaches, and almost all of these patients are heavy smokers. In addition, there may be an increased incidence of thyroid disease. Patients with variant angina may be diagnosed as neurotics or as having an anxiety reaction because of the transient nature of the symptoms and the fact that the angina occurs in a lower risk group for coronary artery disease. The diagnosis is established by recording ST segment shifts on electrocardiogram (ECG) during episodes of chest pain or by showing reversible spasm during coronary arteriography.

Unstable Angina Pectoris

Studies at Stanford[17,18] and by Maseri and coworkers[19] have clearly shown that patients with rest or nocturnal pain due to severe occlusive coronary disease have episodes of angina pectoris unrelated to increases in myocardial work or oxygen demand. Berndt and associates[18] from Stanford reported that, in patients admitted to the coronary care unit with unstable angina pectoris, there was little rise in the double or triple product (heart rate × blood pressure or heart rate × blood pressure × ejection time) at the very earliest onset of resting chest pain compared with resting values. This implies angina in the presence of no increase in myocardial oxygen demands. Furthermore, the little or no change in the double product was in marked contrast to the double product at the onset of pacing-induced angina, where there was approximately a 50 percent rise in double product before these same patients experienced angina associated with typical ST segment depression. These observations have been further documented by Maseri and colleagues[19] by repeat coronary arteriography in patients with unstable angina pectoris in whom transient occlusion in areas of previous occlusive disease have been reported during pain episodes. These clinical studies documenting vasoreactivity and superimposed focal spasm in areas of occlusive coronary disease have established the important role of coronary spasm in unstable angina pectoris or in patients with rest or nocturnal angina. The anginal pain of unstable angina pectoris tends to be characteristic of myocardial ischemia, with typical pain location and radiation pattern. However, the anginal pain may be less responsive to a single nitroglycerin tablet taken sublingually and require more intensive nitrate or calcium-blocker therapy. It is important in these patients as well

to record transient episodes of ST segment depression or elevation as objective proof of myocardial ischemia causing the rest or nocturnal pain.

It is now believed that transient complete coronary obstruction associated with ST segment elevation may be much more common than previously suspected in patients with unstable angina pectoris. For example, most of the patients in the National Heart, Lung, and Blood Institute trial for unstable angina had rest angina.[20] Furthermore, 25 percent had ST segment elevation during one or more chest pain episodes.[21] It is now appreciated that continuous ECG monitoring and, if at all possible, 12-lead electrocardiograms during chest pain are essential to document the ST segment shifts and to assist in locating the area of myocardial ischemia. Thus, the primary difference of these patients from those with classic variant angina is that they have moderate to severe underlying occlusive coronary disease and frequently have effort angina as well. Unless a patient is hypertensive or is having paroxysmal tachycardias as the cause of rest pain, we now believe that superimposed spasm may play a causal role in the unstable or preinfarction state.

Effort Angina

Coronary artery spasm may play a role in patients with typical effort angina, even when there is no rest or nocturnal component. Yasue and colleagues[22] have described the occurrence of spasm in patients with effort-induced angina when ST segment depression was present. This existence of "inappropriate" coronary artery spasm during effort angina remains primarily a theoretic concept, however, because reversal or prevention of spasm with nitrates or calcium antagonists does not permit a higher maximal myocardial oxygen demand or workload at the end of exercise. Variability in episodes of angina on a day-to-day basis and the presence of "walk-through angina" may be partially explained on the basis of inappropriate coronary artery spasm. It is likely, however, that coronary artery spasm plays a minimal role in patients with typical predictable angina of effort.

Diagnostic Methods

Once the diagnosis of coronary artery spasm is suspected in a patient with typical or atypical chest pain, it is helpful for the clinician to ask a series of questions regarding the proper approach to diagnosis in the patient.

- Is the chest pain characteristic of myocardial ischemia? Generally the presenting chest discomfort or anginal syndrome should be typical for angina pectoris in its substernal location, with radiation into the jaw or down the inner aspect of either arm. It may be associated with shortness of breath, palpitations, dizziness or even syncope. The pain should also be relieved by nitroglycerin if coronary spasm is playing an important causal role. Differential diagnosis in patients with rest pain includes a variety of gastrointestinal and chest wall pain syndromes.

- Have ECG changes been recorded with an episode of chest pain? Although it is likely that subtotal or minimal degrees of focal spasm may occur without chest pain or symptoms, it is important to record ST segment shifts on the electrocardiogram to be sure that the asymptomatic episodes are related to myocardial ischemia. For a clear-cut diagnosis, we require transient ST segment depression or elevation of over 0.1 mV for 0.08 seconds if at all possible. As will be discussed, a full 12-lead electrocardiogram can be extremely helpful in documenting ST segment shifts and determining the location of the myocardial ischemia. After administration of nitroglycerin it is useful to report whether these ST segment shifts return to baseline.

- Is the coronary spasm superimposed on severe occlusive coronary artery disease? The diagnosis of severe occlusive coronary artery disease should be suspected in a patient who has rest or nocturnal angina, with a history of effort-induced angina. This is particularly true in a patient with a high prevalence of coronary artery disease risk factors. In patients with this background, it is important not only to treat pain episodes, but to document the severity and extent of occlusive coronary disease.

- Could any of the patient's symptoms be due to arrhythmias? Coronary spasm is well known to produce a wide variety of atrial and ventricular arrhythmias. For example, spasm of the right coronary artery may cause episodes of complete heart block due to ischemia of the atrioventricular (AV) node. These patients may have transient chest pain followed by syncope or transient dizziness. In other patients, ventricular tachycardia or frequent premature ventricular contractions related to myocardial ischemia have been reported and

may precipitate symptoms of palpitations, dizziness or syncope as well. It is essential to relate a patient's chest pain or spasm to these arrhythmias because they are poorly responsive to traditional antiarrhythmic therapy and require prophylaxis or treatment of focal spasm.

Outpatient Approach to Diagnosis

DR. GINSBURG: Because it is essential to record ST segment shifts during episodes of chest pain that may be transient and unpredictable in nature, diagnosis in hospital or on an outpatient basis can be difficult to achieve. It is helpful to attempt initially to record ST segment shifts in patients suspected of coronary spasm on an outpatient basis in an effort to characterize both the frequency and location of the suspected myocardial ischemia (Table 1).[23]

Ambulatory ECG Monitoring

ECG monitoring for 24 to 48 hours may provide important diagnostic clues to a patient's problem by showing not only ST segment shifts, but also arrhythmias during symptomatic or asymptomatic periods of myocardial ischemia. This approach allows for the long-term continuous ECG monitoring that can be important in the outpatient diagnosis when a patient is having at least one episode of pain a day. In addition, the event marker on the ambulatory monitor and a patient diary permit correlation between symptoms and ST segment changes on the electrocardiogram. We use a two-channel recorder that has a sufficiently low frequency response (0.05 Hz) to detect 0.1 mV changes and ST segment shifts (Instruments for Cardiac Research, Inc., New York, ICR Model 7201 and Scanner ICR Model 6201G-2b). It is important to record both channels of the ECG, an inferior and an anterior lead, to be able to see all possible changes of an ST segment shift during pain. This information can be very helpful also in subsequent inpatient studies if the suspected coronary artery involved in spasm can be identified. In addition, we have observed a number of patients with right coronary artery spasm who have transient episodes of second-degree or complete heart block associated with periods of dizziness or syncope without chest pain (Figure 2).

The scanning technician must be made aware that transient ST segment shifts are one of the primary reasons for an ambulatory Holter recording. All symptomatic episodes should have careful analysis of simultaneous periods of ECG recording for either ST depression, ST elevation or return to normal of T wave inversion. Figure 2 shows an example of transient heart block due to right coronary artery spasm that was unassociated with chest pain and led to the correct diagnosis of spasm.

Self-Initiated Transtelephonic ECG Monitoring

In a patient with infrequent and unpredictable episodes of chest pain, it may be difficult to record

TABLE 1.—*Noninvasive and Invasive Evaluation of Coronary Artery Status*

Noninvasive
Detailed history and physical
Electrocardiographic monitoring
Two-channel continuous ambulatory monitor with chest pain diary
In-hospital 12-lead ECG during and after pain
In-hospital continuous telemetry
Self-initiated transtelephonic monitoring during pain
Invasive
Coronary arteriography (off all medications) with ergonovine provocation

ECG = electrocardiogram

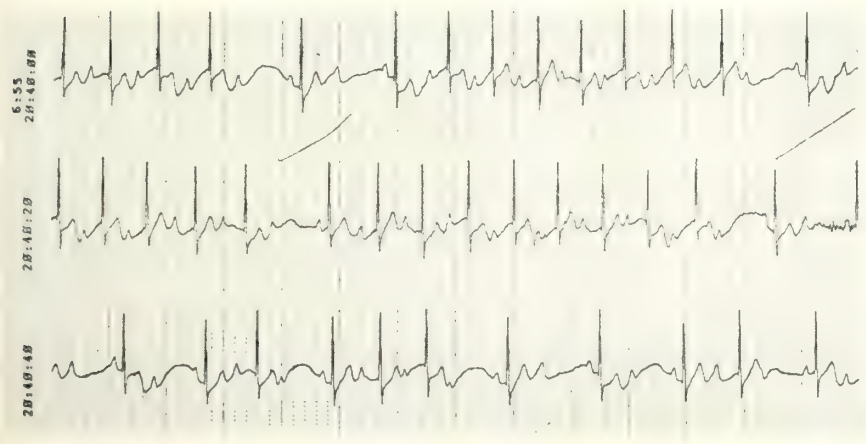

Figure 2.—Computer printout of Holter electrocardiogram recording showing transient second degree heart block.

ST segment shifts by 24- or 48-hour ambulatory ECG monitoring. For these patients we have been using the Cardiobeeper (Survival Technology, Bethesda, MD), which is a bipolar-lead system with a low frequency response for transmission of electrocardiograms.[24] Patients are instructed to keep the ECG electrodes attached to their chest at all times. When an episode of chest pain occurs, they can quickly attach the leads to the previously attached electrodes and, by any available telephone, transmit an electrocardiogram during a pain episode. The single-lead electrocardiogram is then tape recorded for later conversion to a rhythm strip for review and analysis. Figure 3 shows a typical episode of ST segment elevation that was transmitted and compared with a previously transmitted baseline electrocardiogram during a pain-free period. The primary advantage of this system is its use in patients with cyclic or infrequent episodes of pain and the fact that it can be used relatively inexpensively over long periods of time. The primary disadvantage is that it is a single-channel recorder and may miss ST segment changes in other leads and will miss arrhythmias or ST segment shift when a patient is not symptomatic.

Treadmill Exercise Testing

When evaluating a case of suspected focal coronary artery spasm, it is helpful to ascertain whether a patient may have underlying occlusive coronary disease as well. For this reason a treadmill exercise test, during which time repeated 12-lead electrocardiograms can be recorded, is very helpful in an outpatient evaluation. Patients with typical variant angina pectoris and normal coronaries generally have excellent exercise tolerance with no ST segment shifts or pain during maximal exercise. A small percentage of these patients may have postexercise chest pain and ST segment elevation or depression, possibly due to autonomic disturbance during recovery from exercise. In a patient in whom typical effort angina develops with ST segment depression, the clinical impression of occlusive artery disease, possibly with superimposed spasm, can be established. Outpatient testing using ECG monitoring and treadmill exercise test does not necessarily supplant the need for inpatient evaluation and coronary arteriography but will provide a basis for the suspected role of spasm in a patient and assist in locating the responsible coronary artery. Furthermore, the recording of arrhythmias during symptomatic or asymptomatic periods of spasm may help explain previously unexplained symptoms before hospital admission.

In-hospital Diagnostic Approach

Because rest or nocturnal angina may be a symptom of severe occlusive coronary artery disease or preinfarction angina, it is important to proceed with hospital evaluation and coronary arteriography, if this has not been previously accomplished. It is extremely helpful to be able to observe patients in hospital during an episode of chest pain, at which time a 12-lead electrocar-

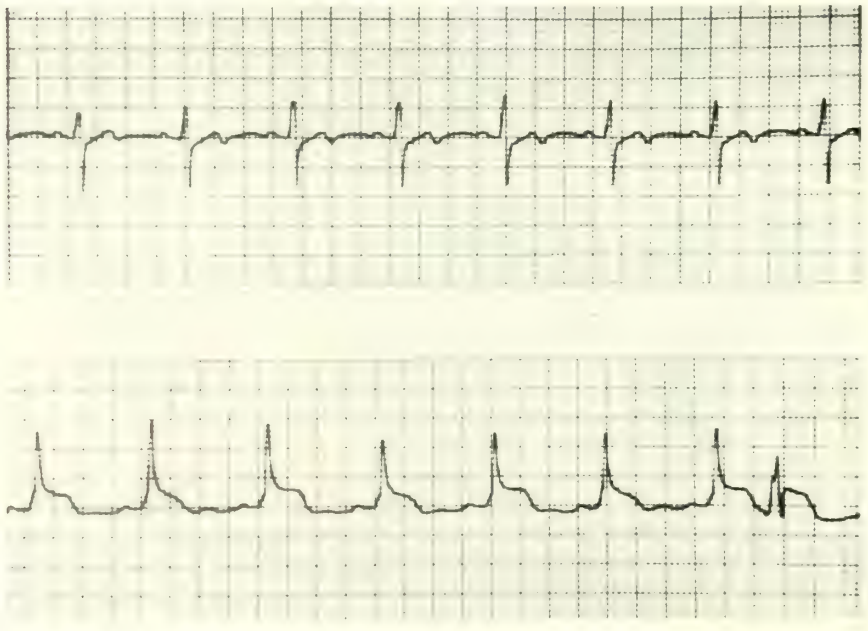

Figure 3.—Rhythm strip from transtelephonic transmission of electrocardiogram. The top strip is a baseline recording while patient is free of pain. The bottom strip shows ST segment elevation during episode of chest pain.

diogram can be obtained before they take nitroglycerin. Orders must be clearly written requesting a stat electrocardiogram during chest pain and not allow any symptomatic treatment of the chest pain before recording the ST segment shift. Figure 4 shows a 12-lead electrocardiogram during moderately severe episodes of chest pain and return to baseline three hours later. A patient with nocturnal episodes of chest pain can be attached at bedtime to a three-lead automatic ECG machine and instructed to push the automatic start button to record the electrocardiogram when awakened by chest pain. This approach does not depend on other medical personnel while the patient is having acute chest pain and it facilitates the recording of ST segment shift and allows earlier taking of medication for relief of symptoms.

Ergonovine Provocation During Coronary Arteriography

DR. SCHROEDER: A carefully planned coronary arteriogram in a patient with suspected coronary spasm nearly always provides conclusive answers. It allows determination of the extent of fixed atherosclerotic occlusive coronary disease and whether focal spasm may be playing a role. Before coronary arteriography, patients are tapered off all long-acting nitrates, nitroglycerin ointment formulations, beta blockers and calcium antagonists. Patients are permitted to take nitrate sublingually for episodes of chest pain as needed, but if at all possible no other cardiovascular medications are used. Premedication should be minimal and no antihistamines given. It is essential to obtain consent not only for coronary arteriography but for ergonovine administration before arteriography is done.

First routine coronary arteriography is done. If the coronary arteries are normal or have insufficient fixed occlusive disease to explain a patient's rest angina symptoms, ergonovine maleate testing is then undertaken.[11,25] Radiolucent electrode pads are placed on the chest wall for a complete 12-lead electrocardiogram and a 3-channel, 12-lead ECG machine is attached. The protocol for ergonovine challenge is outlined in

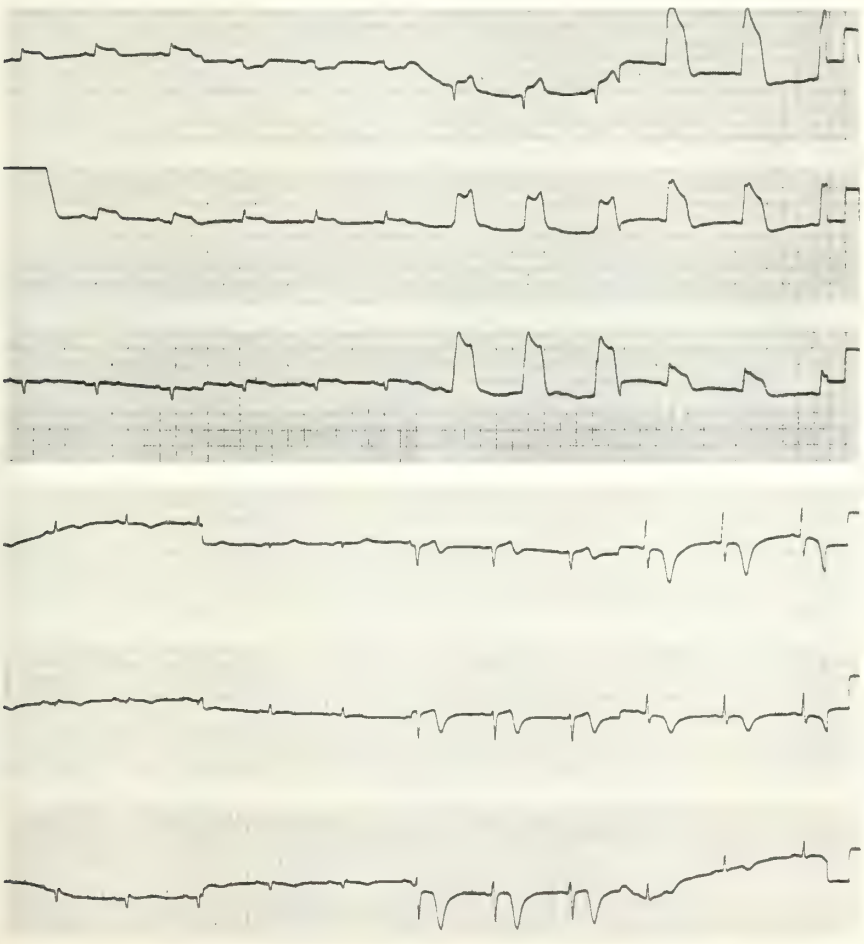

Figure 4.—Twelve-lead electrocardiogram strip taken during chest pain showing pronounced ST segment elevation in the anterolateral leads **(top)** and three hours after resolution of the pain **(bottom).**

Table 2. A solution of nitroglycerin must be made up before initiation of the provocative testing to allow expeditious treatment of any induced spasm (Table 3). If there is a history of possible heart block associated with the pain as indicated by symptoms or by previous ECG monitoring, a right ventricular pacing wire should also be positioned. If the Judkin's technique for coronary arteriography is being used, the catheter for the artery most suspected of spasm should remain in position during the ergonovine testing.

The ergonovine is given by intravenous bolus in three doses: 0.05 mg, 0.1 mg and 0.25 mg. It is absolutely essential to allow at least three minutes after each bolus injection during which time an ECG is taken at 1½ and 3 minutes. If chest pain develops or there are ECG changes compatible with ischemia, a coronary artery injection is made. It may be necessary to exchange catheters quickly with the Judkin's technique if the first one does not show spasm but there are clear-cut ST segment shifts in another area on the electrocardiogram. If pain or ST segment shifts do not occur after the final dose, each coronary artery must be reinjected because occasionally subtotal focal occlusion may occur without major symptoms or ST segment shifts. If there are no symptoms or ECG changes and at least five minutes have gone by since the last injection of ergonovine, nitroglycerin should be given and the study completed.

If focal spasm is recorded, it is essential not to repeat injections of contrast material into various angles of the occluded artery. The spasm can be reversed with intravenous administration of nitroglycerin. In difficult cases nitroglycerin can be administered intracoronary in an initial dose of 0.05 to 0.1 mg and repeated one to three times with the patient monitored for hypotension.

TABLE 2.—*Protocol for Ergonovine Challenge*

Obtain informed consent

No premedication

Prepare ergonovine and nitroglycerin for intravenous administration

Crash cart available

Minimum Interval Time (minutes)	*Dose of Ergonovine (mg)*	*Obtain Electrocardiogram*
0.0		✓
	0.05 (1 ml)	
1.5		✓
3.0		✓
	0.1 (2 ml)	
4.5		✓
6.0		✓
	0.25 (5 ml)	
7.5		✓
9.0		✓

Stop test as soon as chest pain or ST segment shift occurs

Reverse spasm with sublingual, intravenous or intracoronary administration of nitroglycerin as soon as documented

TABLE 3.—*Preparing Drugs for Ergonovine Provocation Test*

Prepare ergonovine

- Fill 10 ml syringe with 0.4 mg (2 ml) ergonovine maleate (Ergotrate, Eli Lilly and Co.) and 6 ml sterile water
- Final concentration: 0.05 mg per ml

Prepare nitroglycerin for intravenous administration

- Drop two 0.4 mg nitroglycerin tablets inside 10 ml syringe
- Fill syringe with 8 ml sterile water, replace barrel of syringe and shake
- Place Millipore filter (Milex®-GI, Millipore Corp., Bedford, MA) on end of syringe
- Final concentration: 100 μg per ml (must be prepared fresh each time)

Interpretation of Results

Cipriano and colleagues[25] have shown that there is a normal dose-related response of coronary arteries to ergonovine provocation. Generally, diffuse narrowing of less than 20 percent occurs (Figure 5). In patients with normal or essentially normal coronary arteries, diffuse or focal spasm with over 70 percent occlusion of the lumen is consistent with coronary artery spasm (Figure 6). However, unless there are accompanying symptoms of chest pain typical of a patient's pain pattern or ECG changes consistent with myocardial ischemia —whether it be ST depression or ST elevation— the diagnosis is not firmly established. We believe that it is safe to administer ergonovine in patients with occlusive coronary disease as long as the severity of the lesions does not explain their rest pain, that is, generally less than 50 percent occlusion. In these patients, focal spasm is usually observed in an area of atherosclerotic disease and should also cause an observed 70 percent or more reduction in luminal size. Focal spasm is confirmed by associated chest pain and evidence of myocardial ischemia on the electrocardiogram. The administration of ergonovine to patients with severe fixed obstructive disease is dangerous and may provoke myocardial infarction. Once recorded, spasm should be reversed as soon as possible as previously discussed.

Studies with ergonovine provocation at Stanford

University Medical Center and the University of Florida have documented the safety and reproducibility of this test.[11,26,27] In patients with typical variant angina without fixed obstruction, it appears to be specific and sensitive. In patients who are not suspected of having coronary spasm or who have atypical chest pain related to mitral valve prolapse, chest pain may be observed in 10 percent to 20 percent of cases but without associated ST segment shifts or focal spasm seen on arteriography. The risk of this procedure is in inducing spasm with associated myocardial ischemia and potential arrhythmias. A small number of deaths have been reported and in most cases were due to the injudicious use of large initial doses of ergonovine, not waiting an adequate time between doses or not documenting focal spasm because of lack of symptoms, or not being prepared to reverse spasm with intravenous or intracoronary administration of nitroglycerin.[28]

Outpatient testing with ergonovine in the same cautious, systematic manner can be done in patients who have had previously documented normal coronary arteries and who do not have symptoms of syncope or dizziness that might reflect heart block or ventricular tachycardia. In these patients an intravenous line should be started and blood pressures taken regularly. Ergonovine and nitroglycerin are prepared as previously described.

We consider the ergonovine study to be positive if there are electrocardiographic changes of ST segment elevation or depression of 0.1 mm or more associated with chest pain that is similar to a patient's usual pain pattern. As soon as a patient has chest pain and associated ST segment shifts, nitroglycerin is administered intravenously

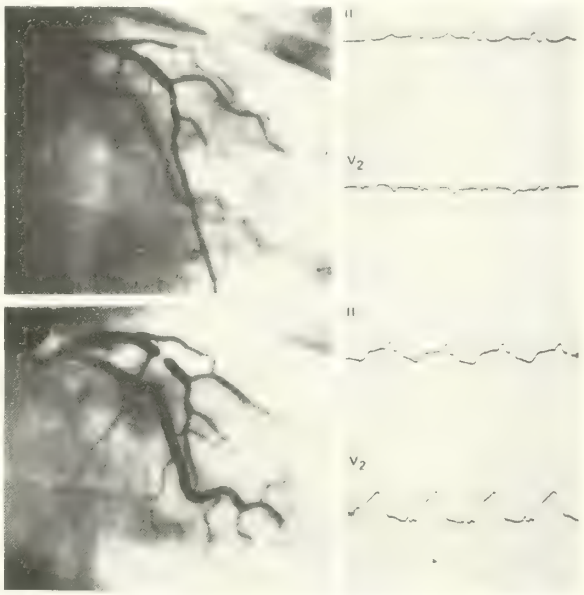

Figure 6.—Photographs and rhythm strips of left coronary arteriogram showing normal vessels in top panel and pronounced focal spasm of the left anterior descending artery with associated ST segment elevation in lead V_2 in the lower panel.

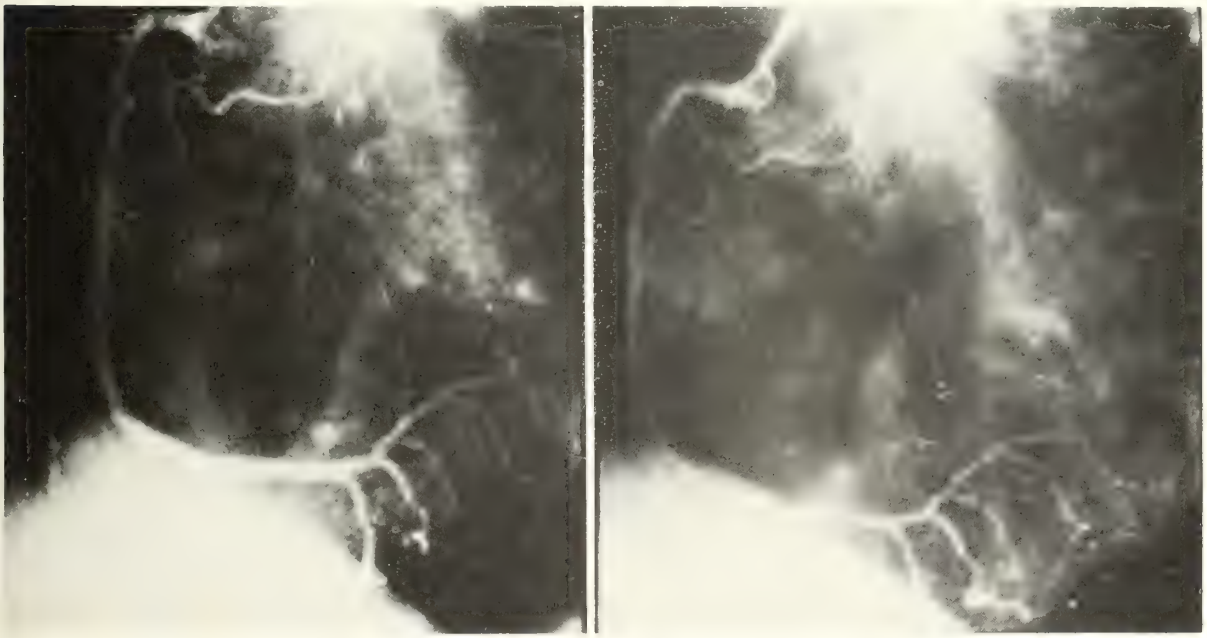

Figure 5.—Photographs of coronary arteriogram of the right coronary artery during control **(left)** and after administration of 0.25 mg of ergonovine maleate showing the diffuse 20 percent narrowing of the artery **(right).**

(50 to 100 μg). The patient should be carefully monitored for hypotension or continued ischemia and given additional nitroglycerin intravenously as necessary. A patient is monitored and observed until the ECG findings return to normal.

Treatment of Coronary Artery Spasm

DR. GINSBURG: Since 1979 a clinic devoted solely to the evaluation and treatment of suspected coronary artery spasm has been in operation at Stanford University Medical Center. From our experience in this clinic we have developed a program for treating patients with coronary spasm (see Table 4). This treatment is based on both understanding the underlying pathogenetic mechanisms and detailing the clinical symptoms. The extent of underlying pathology (atherosclerosis) in the coronary arteries of our patients varies greatly from those free of obstructive disease with vasospasm to those with severe atherosclerotic disease and a concomitant vasospastic component. The approach to the treatment of these patients involves a synthesis of both underlying pathology and clinical symptoms. The final common pathway for treating a patient with angina is to reduce myocardial ischemia by improving flow of oxygenated blood, decreasing demand for it or some combination of the two.

The specific treatment of coronary artery spasm includes the following:

Nitrates

Nitroglycerin is the most effective agent available for aborting acute bouts of spasm and for prophylaxis. The method of administration of nitrates depends on the clinical situation. Prophylactic treatment for spasm incorporates the use of long-acting nitrates such as isosorbide dinitrate (20 to 240 mg a day), time-suspension capsules (5 to 10 mg a day) or nitroglycerin paste (1 to 12 inches a day). Sublingual nitroglycerin (0.3 to 0.6 mg) can be used effectively by patients to abort episodes of chest pain.

In patients who have coronary artery spasm provoked by pharmacologic agents such as ergonovine, intravenously administered nitroglycerin (50 to 150 μg bolus) should be given. In the catheterization laboratory nitrates can be administered either intravenously or into the coronary artery (100 to 300 μg). It should be remembered that spasm can occasionally be refractory to nitroglycerin and up to 1 mg a minute may sometimes have to be administered intravenously.

Calcium Entry Blockers

Calcium blockers, including diltiazem hydrochloride, nifedipine and verapamil, are the agents

TABLE 4.—*Treatment of Coronary Artery Spasm*

	Drugs
On Basis of Mechanisms	
Coronary spasm without significant obstructive coronary artery disease	Nitrates and/or calcium blockers
Coronary spasm with significant obstructive disease	1. Ca blockers alone or 2. Ca^+ blockers + beta blockers or 3. Ca^+ blockers + coronary bypass surgery

Drug	*Dose*	*Major Side-Effects*
Pharmacologic Agents		
Administration of nitrates		
Sublingual	0.3-0.6 mg	Hypotension; headache
Paste	1-12 in/day	Hypotension; headache
Oral	20-120 mg/day	Hypotension; headache
Intravenous	50-150 μg bolus	Hypotension; headache
Intracoronary	100-300 μg bolus	Hypotension; headache
Calcium blockers		
Diltiazem* (Cardizem)	240-360 mg/day	None
Nifedipine† (Procardia)	30-180 mg/day	Hypotension; pedal edema
Verapamil‡ (Isoptin)	80-480 mg/day	Constipation
Phentolamine hydrochloride (Regitine)		Not useful
Phenoxybenzamine hydrochloride (Dibenzyline)		Not useful
Propranolol hydrochloride (Inderal)		Not useful
Metoprolol tartrate (Lopressor)		Not useful

*Not available in the United States.
†Available in the United States as an oral preparation only.
‡Available in the United States as an intravenous solution only.

of choice in treating coronary spasm. Orally given nifedipine and intravenously given verapamil are now available. Diltiazem and an oral preparation of verapamil should be released soon by the Food and Drug Administration.

Although these three drugs are grouped under the general heading of calcium entry blockers, each drug has its own specific pharmacologic and pharmacokinetic mechanisms of action and adverse reactions. Each drug has specific clinical indications and relative contraindications. Understanding their pharmacologic activity is essential for administration. Each agent's effectiveness is also dependent on the underlying pathophysiology of the patient's clinical symptoms.

Diltiazem.[29] This agent's primary action is on the coronary artery bed, so it is effective in the treatment of spasm. The usual dosage is 240 to 360 mg a day given in divided doses every six hours. Adverse reactions have been almost nonexistent at these dosages. Diltiazem can be given safely with beta blockers or nitrates. Relative contraindications include AV conduction disease or severe left ventricular failure.

Nifedipine.[30] This agent has also proved effective in treating coronary spasm. Nifedipine is given in dosages of from 30 to 180 mg a day. It has no effect on the conduction system but does dilate the peripheral arterial bed and the coronary arteries. Thus the drug is also useful in severe hypertension or in reducing peripheral vascular resistance. Side effects include orthostatic hypotension, reflex tachycardia and pedal edema. Nifedipine can be given safely with beta blockers and nitrates and to patients with congestive heart failure.

Verapamil.[31] Verapamil is a very effective agent in the treatment of coronary spasm, as well as in the treatment of supraventricular arrhythmias. Dosages are from 80 to 480 mg a day, given on an every-six-hour dose schedule. Verapamil should not be used in patients with conduction disease or congestive heart failure. Side effects include nausea, vomiting and constipation. Verapamil can be given along with nitrates and beta blockers if there is no conduction disease or failure.

Membrane Receptor Blockade

The pathologic mechanism of coronary spasm is most likely due to an abnormality beyond the level of a single membrane receptor. Therefore, specific receptor blockage with α-, β-, muscarinic or histaminic antagonists would not be expected to be effective. Experience with phentolamine or phenoxybenzamine hydrochloride has shown that these agents are only occasionally effective and and not without significant side effects. They probably operate by their nonspecific vasodilating properties. Beta blockers are also not useful in the treatment of coronary spasm as they have no vasodilator action. However, this should be clarified with respect to patients who have spasm superimposed on hemodynamically significant stenosis. In these patients a combination of calcium blockers (to treat spasm) and beta blockers (to decrease myocardial demand) is very useful and effective therapy.

Surgical Denervation

Complete or partial denervation of the human heart is an interesting procedure historically in the treatment of spasm but has no place in the present treatment of spasm.

Risk Factor Reduction

Coronary spasm nearly always occurs in areas of atherosclerosis, regardless of the degree. Therefore, aggressive attempts should be made to decrease risk factors. This is especially true of cigarette smoking, since our experience has been that 85 percent to 90 percent of patients with spasm are cigarette smokers. Blood pressure should be kept under control and weight reduction and lowering of cholesterol attempted.

Pacemakers

Arrhythmias are quite common in patients during periods of active spasm. These arrhythmias, such as AV block, sinus bradycardia and ventricular tachycardia or fibrillation, are secondary events due to ischemia. Treatment of these arrhythmias consists of prevention because if coronary spasm is prevented by aggressive treatment, then arrhythmias are not a problem. Pacemaker insertion is not indicated for bradycardia or AV block due to spasm unless these phenomena are the result of processes unrelated to spasm.

REFERENCES

1. Prinzmetal M, Kemnamer R, Merliss R, et al: Angina pectoris—I. The variant forms of angina pectoris. Am J Med 1959; 27:375

2. Osler W: The Lumleian Lectures on angina pectoris. Lancet 1910; 1:699

3. Wilson F, Johnston F: The occurrence in angina pectoris of electrocardiographic changes similar in magnitude and in kind to those produced by myocardial infarction. Am Heart J 1941; 22:64

4. Ginsburg R, Bristow MR, Harrison DC, et al: Studies with isolated human coronary arteries. Chest 1980 Jul; 78(Suppl):180-186

5. Ricci DR, Orlick AE, Cipriano PR, et al: Altered adrenergic activity in coronary arterial spasm: Insight into mechanism based on study of coronary hemodynamics and the electrocardiogram. Am J Cardiol 1979 Jun; 43:1073-1079

6. Robertson D, Robertson RM, Nies A, et al: Variant angina pectoris: Investigation of indexes of sympathetic nervous system function. Am J Cardiol 1979 Jun; 43:1080-1085,

7. Bertrand ME, Lablanche JM, Talment PY, et al: Complete denervation of the heart (autotransplantation) for treatment of severe refractory coronary spasm. Am J Cardiol 1981; 47:1376-1378

8. Clark DA, Quint RA, Mitchell RL, et al: Coronary artery spasm: Medical management, surgical denervation, and autotransplantation. J Thorac Cardiovasc Surg 1977 Mar; 73:332-339

9. Buda AJ, Fowles RE, Schroeder JS, et al: Coronary artery spasm in the denervated transplanted human heart. Am J Med 1981; 70:1144-1148

10. Robertson RM, Robertson D, Roberts LJ, et al: Thromboxane in vasotonic angina pectoris with evidence from direct measurements and inhibitor trials. N Engl J Med 1980; 304: 998-1003

11. Schroeder JS, Bolen JL, Quint RA, et al: Provocation of coronary spasm with ergonovine maleate—New test with results in 57 patients undergoing coronary arteriography. Am J Cardiol 1977 Oct; 40:487-491

12. Endo M, Hirosawa K, Kaneko N: Prinzmetal's variant angina—Coronary arteriogram and left ventriculogram during angina attack induced by methacholine. N Engl J Med 1976 Jan 29; 294:252-255

13. Yasue H, Touyama M, Shimamoto M, et al: Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. Circulation 1974 Sep; 50:534-539

14. Yasue H, Nagao M, Omote S, et al: Coronary arterial spasm and Prinzmetal's variant form of angina induced by hyperventilation and Tris-buffer infusion. Circulation 1978 Jul; 58:56-62

15. Ginsburg R, Bristow MR, Kantrowitz N, et al: Histamine provocation of clinical coronary artery spasm: Implications concerning pathogenesis of variant angina pectoris. Am Heart J 1981; 102:819-822

16. Allaire BI, Schroeder JS: Prinzmetal's angina—Clinical and anatomic aspects. West J Med 1975 Mar; 122(3):187-193

17. Cannom DS, Harrison DC, Schroeder JS: Hemodynamic observations in patients wtih unstable angina pectoris. Am J Cardiol 1974 Jan; 33:17-22

18. Berndt TB, Fitzgerald J, Harrison DC, et al: Hemodynamic changes at the onset of spontaneous versus pacing-induced angina. Am J Cardiol 1977 May 26; 39:784-788

19. Maseri A, L'Abbate A, Baroldi G, et al: Coronary vasospasm as a possible cause of myocardial infarction—A conclusion derived from the study of preinfarction angina. N Engl J Med 1978 Dec 7; 299:1271-1277

20. Russell RO, Karp R, Resnekov L, et al: Unstable angina pectoris: National cooperative study group to compare medical and surgical therapy—I. Report of protocol and patient population. Am J Cardiol 1976; 37:896-908

21. Schroeder J, Russell R, Resnekov L, et al: Unstable angina pectoris: National randomized study of surgical versus medical therapy—Results in Prinzmetal-type angina. Am J Cardiol 1978; 41:397-402

22. Yasue H, Omote S, Takizawa A, et al: Exertional angina pectoris caused by coronary arterial spasm—Effects of various drugs. Am J Cardiol 1979 Mar; 43:647-652

23. Ginsburg R, Schroeder JS: Coronary artery spasm: Approach to diagnosis and treatment. Practical Cardiology 1980; 24-34

24. Ginsburg R, Lamb I, Schroeder JS, et al: Long-term transtelephonic electrocardiographic monitoring in the detection and evaluation of variant angina. Am Heart J 1981; 102:196-201

25. Cipriano PR, Gunthaner DF, Orlick AE, et al: The effects of ergonovine maleate on coronary arterial size. Circulation 1979; 59:82-89

26. Curry RC Jr, Pepine CJ, Sabom MB, et al: Effects of ergonovine in patients with and without coronary artery disease. Circulation 1977 Nov; 56(5):803-809

27. Curry RC Jr, Pepine CJ, Sabom MB, et al: Similarities of ergonovine-induced and spontaneous attacks of variant angina. Circulation 1979 Feb; 59(2):307-312

28. Buxton A, Goldberg S, Hirschfeld JW, et al: Refractory ergonovine-induced coronary vasospasm: Importance of intracoronary nitroglycerin. Am J Cardiol 1980 Aug; 46(2):329-334

29. Rosenthal SJ, Ginsburg R, Lamb I, et al: Efficacy of diltiazem for control of symptoms of coronary arterial spasm. Am J Cardiol 1980; 46:1027

30. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-spasm—Experience in 127 patients. N Engl J Med 1980 Jun 5; 302:1269-1273

31. Johnson SM, Mauritson DR, Hillis LD, et al: Verapamil in the treatment of Prinzmental's variant angina: A long-term, double-blind, randomized trial, abstracted. Am J Cardiol 1981; 47:399

Refer to: Cogan MG: Nephrotic syndrome—Medical Staff Conference, University of California, San Francisco. West J Med 1982 May; 136:411-417

Medical Staff Conference

Nephrotic Syndrome

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *In this Medical Grand Rounds we will discuss the nephrotic syndrome. Dr. Martin Cogan will lead the discussion.*

DR. COGAN:† It has been roughly ten years since the nephrotic syndrome was last discussed in these conferences.[1] This discussion will focus on advances in pathophysiology, pathogenesis and treatment of the nephrotic syndrome in the past decade.

Definition

The nephrotic syndrome is commonly described to encompass five clinical features: hyperalbuminuria, hypoalbuminemia, hyperlipidemia, hyperlipiduria and edema.

The first, *hyperalbuminuria,* is the cardinal feature of the syndrome, without which the diagnosis cannot be made. Protein excretion of 3.5 grams per 24 hours is usually accepted as the minimal level for nephrotic-range proteinuria and leads consecutively and in varying degrees to the other four features.[2] Most of the following discussion will relate to the pathophysiology and pathogenesis of the increased albumin excretion. But, first, a brief presentation is in order regarding the secondary features that result from proteinuria.

Hypoalbuminemia results from the abnormally high urinary protein excretion. As proteinuria develops, hepatic synthesis of albumin is augmented, but the increase is not enough to cause the albumin concentration of the blood to return to normal. Maximal rates of albumin synthesis by the liver are estimated to be about twice the normal production of 12 to 14 grams per day (representing about 4 percent of the total albumin pool in the body). There is also increased albumin catabolism by the kidney in nephrosis in addition to urinary excretion. Besides albumin, there are many other proteins lost in the urine in patients with nephrotic syndrome and consequently a decline in blood levels of these proteins.[3] The urinary loss of antithrombin III has been associated with the thromboembolic tendency of the nephrotic syndrome, including renal vein thrombosis. Increased excretion of complement factor B with impaired complement-dependent opsonization of some bacteria presumably accounts for the increased susceptibility of patients with nephrotic syndrome to pneumococcal disease. There is increased urinary excretion of high-density lipoprotein (HDL, a constituent of the oval fat bodies observed in nephrotic urine); of transport proteins for iron, copper and zinc; of orosomucoid (which has also been implicated in the hyperlipidemia of the nephrotic syndrome); of immunoglobulin G; of procoagulant proteins, especially factors IX, XI and XII (which can rarely lead to a hemor-

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†Martin G. Cogan, MD, Assistant Professor of Medicine.

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
DEAE = diethylaminoethyl dextran
HDL = high-density lipoprotein
LDL = low-density lipoprotein
VLDL = very low-density lipoprotein

rhagic rather than thromboembolic tendency), and, finally, of transport proteins for hormones like thyroxine, cortisol and vitamin D, usually not of clinical importance.

Hyperlipidemia and the consequent *hyperlipiduria* occur due to an increase in lipoprotein synthesis, especially low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL), with an increase in blood cholesterol. Triglyceride levels are variably elevated and HDL, due to enhanced urinary excretion, is decreased. The ratio of the levels of HDL to LDL and VLDL is, therefore, diminished, a situation that has been suggested to accelerate atherogenesis. However, large retrospective studies of 159 patients in London[4] and 125 patients in San Francisco[5] have failed to confirm the existence of increased atherogenetic events associated with the nephrotic syndrome. Hyperlipidemia appears to be caused by hypoalbuminemia and decrease in oncotic pressure of the blood and can be reversed—at least transiently—by intravenous infusion of an oncotic agent, either albumin itself or dextran.[6,7]

Finally, the pathogenesis of *edema* in nephrotic syndrome has generally been ascribed to decrease in the oncotic pressure of the blood. Diminished intravascular colloid osmotic pressure causes fluid transudation into the interstitial spaces of the body. The resulting decrease in plasma volume leads to a slight reduction in the blood pressure and also a stimulation of renin and, hence, aldosterone with secondary renal salt retention. Although attractively simple, this pathogenetic scheme has been recently recognized as insufficient to explain the edema in a third to a half of adults with nephrotic syndrome.[8,9] The first problem is that measured plasma volumes in many nephrotic subjects are normal to increased. Second, blood pressure is normal and sometimes even in the hypertensive range in this substantial fraction of patients with nephrotic syndrome. Finally, renin and aldosterone levels in this subgroup have been found to be suppressed, indicating primary rather than secondary renal salt retention. Therefore, the pathogenesis of edema, at least in some nephrotic patients, remains enigmatic.

Pathophysiology of Hyperalbuminuria

Although significant unresolved questions persist regarding the secondary features of the nephrotic syndrome, there has been substantial progress in understanding the primary feature, albuminuria. Understanding the pathophysiology of albuminuria is dependent on recognition of the factors that normally operate to efficiently exclude albumin from filtration across the glomerular capillary wall. It can be easily calculated that at a normal serum albumin concentration and glomerular filtration rate, a daily urinary excretion of 6 kg of albumin would occur if passage across the glomerular capillary were unrestrained, assuming hepatic synthesis could keep up with this degree of loss, which, of course, it could not. In contrast, a normal urinary albumin excretion rate of 60 mg a day represents only about 10^{-5} of the albumin available for glomerular filtration. In a nephrotic patient with a reduced serum albumin concentration of 2 grams per dl and a half-normal glomerular filtration rate, the urinary albumin excretion of even 14 grams a day represents only 1 percent (10^{-2}) of the albumin that could be filtered. Because albumin is neither substantially reabsorbed[10] nor is it secreted, the question of how much albumin excretion occurs (10^{-2} versus 10^{-5} of the albumin available for filtration) becomes one of how well albumin is prevented from crossing the kidney's filtration barrier, the glomerular capillary wall. Much of our knowledge of the normal restraints to albumin filtration and how such restrictions are lifted, causing enhanced albumin filtration in nephrosis, comes from studies of Barry Brenner and his colleagues in San Francisco and later in Boston.[11,12]

Figure 1 presents a summary of experiments from Dr. Brenner's laboratory that describes the glomerular-sieving characteristics of normal rats and of rats with renal disease.[13] The vertical axis represents the fractional clearance of a solute, which is the clearance of a given molecule compared with that of a freely filtered solute, such as creatinine or inulin. It is assumed that there is neither tubular reabsorption nor secretion of the solute. A fractional clearance of unity means that the clearance of the solute would be 100 percent that of inulin. These fractional clearances are expressed as a function of the effective molecular radius of the solute, the Einstein-Stokes radius,

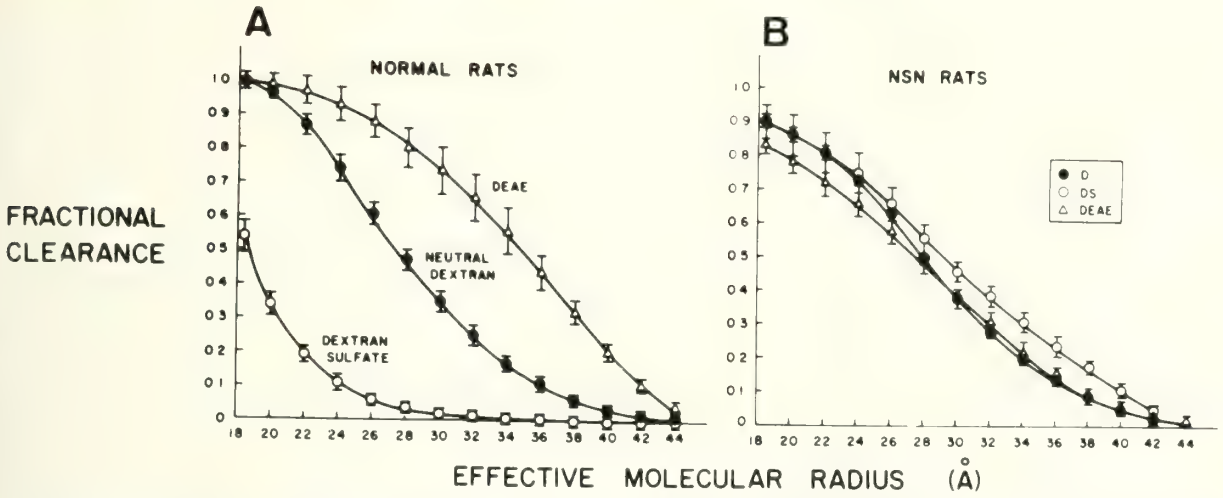

Figure 1.—Fractional clearances (compared with inulin) for positively charged dextran (DEAE), neutral dextran (D) and negatively charged sulfated dextran (DS) in normal rats **(A)** and in rats with glomerulonephritis with proteinuria **(B)** as a function of the effective molecular radius of the dextran. (Reproduced with permission from Bohrer et al.[13]) DEAE = diethylaminoethyl dextran, DS = dextran sulfate.

shown on the horizontal axis. If one first observes the neutral dextran curve given in the solid circles, a neutral dextran molecule with an effective molecular radius of 18 Å or less is filtered just as easily as that of the freely filtered inulin. As the neutral dextran molecular radius increases, there is a progressive diminution in the ability of that dextran to cross the glomerular capillary wall. At a radius of 36 Å, which is the radius of albumin, there is a pronounced reduction in the ability of that dextran to cross the glomerular capillary wall, only about one tenth that of inulin. Yet this 10^{-1} restriction of a neutral dextran based on its size is insufficient to account for the more marked constraint (10^{-5}) on transglomerular albumin movement that normally exists, as described previously. There must, therefore, be another factor besides size preventing passage of albumin into the urine. A likely candidate for such a factor was considered by Dr. Brenner and his group to be molecular charge. If the basement membrane had a prominent anionic charge, then a molecule such as albumin, which also has a strong anionic charge, would be repelled and would not be filtered across the glomerular capillary wall. To support this hypothesis, sulfated dextrans, which have a negative charge (the open circles in Figure 1A), were found to have far less fractional clearances at molecular radii from 20 to 40 Å when compared with the neutral dextrans of similar sizes (closed circles). At 36 Å the filtration of a negatively charged dextran was fully 10^{-2} less than that of a neutral dextran.

The converse effect of charge was also found; namely, positively charged diethylaminoethyl dextran (DEAE, the open triangles in Figure 1A) exhibited enhanced passage through the glomerular wall compared with similarly sized neutral dextran. Thus, the experimental evidence supports the concept that there are two major discriminants of whether a solute can pass through or will be excluded from the glomerular capillary wall: size and charge. Minor discriminants, such as solute configuration and determinants of single nephron glomerular filtration rate, have also been shown.

Dr. Brenner's group went on to examine the dextran-sieving curves in rats with an acute glomerulonephritic process with proteinuria. They reasoned that the albumin might be allowed transit through the glomerular wall not because of an alteration in size discrimination, but rather because the glomerular basement membrane had lost its negative charge and, hence, no longer excluded anionic molecules. Figure 1B shows the loss of charge, but not size, discrimination in nephrotoxic serum nephritis. The neutral sieving curve is similar to normal, but there is no longer preferential inhibition of clearance of negatively charged dextran nor preferential filtration of positively charged dextran (DEAE). Histologic confirmation of these and other physiologic studies[14] was attained by showing that the glomerular basement membrane in nephrotic states had lost the staining properties normally associated with anionic charge.[15,16]

In summary, the experimental evidence has

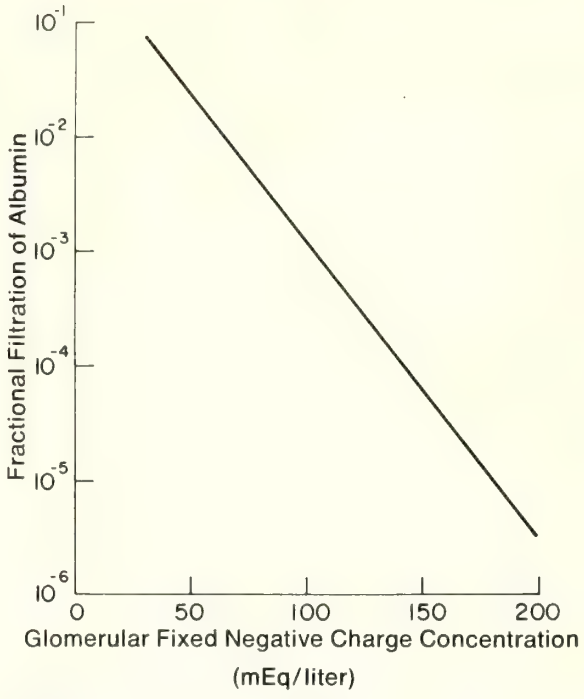

Figure 2.—Theoretical relationship of fractional albumin filtration as a function of the mean fixed negative charge density in the glomerular capillary wall. Albumin is assumed to have a molecular charge of −19. (Redrawn with permission from Deen and Satvat.[17])

grown to support the concept that the principal normal barrier to transglomerular filtration of albumin is the anionic nature of the glomerular basement membrane. Furthermore, the loss of this anionic property results in albumin filtration and albuminuria. A theoretic quantitative treatment of the inverse relationship between glomerular basement membrane anionic charge density and filtration of anionic solutes, such as albumin, has been recently proposed by Deen and Satvat,[17] as illustrated in Figure 2.

Morphologists disagree as to the predominant site of the negative charge in the glomerular basement membrane. Using various stains or isoelectrically focused molecular probes, it has been postulated that the principal anionic glomerular structures responsible for albumin restriction include the basement membrane itself, perhaps with contributions by epithelial slit pores and the "fuzzy coat" of the epithelial cells.[18-20] The chemical nature of the fixed anionic charge is also uncertain, but probably represents sialoglycoproteins, especially heparan sulfate.[18] Another interesting consequence of the high anionic density surrounding the epithelial cells may be the electrostatic repulsion they exert on each other, which is responsible for the normal separation of the epithelial foot processes.[20] If such negative charges were diminished, as can be done experimentally by perfusion with protamine, there is rapid fusion of the foot processes accompanying the proteinuria. Restoration of the glomerular negative charge with heparin then promptly stops the proteinuria and reestablishes foot process integrity.[21,22]

The physiologic and morphologic techniques described above have been extended to humans to verify that the nephrotic syndrome results from disruption of the normal charge discriminatory function of the glomerular basement membrane. Robson and co-workers[23] showed that size discrimination using neutral macromolecules (polyvinylpyrrolidone) was intact or even slightly enhanced in children with the nephrotic syndrome due to nil disease. By inference, the albuminuria was ascribed to loss of glomerular negativity. Carrie and Myers[24] have also shown only slightly altered glomerular sieving on the basis of molecular size in nephrotic adults with nil disease or diabetes. Thus, the experience in humans is consonant with that in animals: The major pathophysiologic factor responsible for albuminuria is a reduction in the glomerular capillary wall anionic charge density.[15]

Pathogenesis of Hyperalbuminuria

In the classic works of Germuth[25] and Dixon and associates,[26] circulating immune complexes were found to temporally correlate with the development of acute glomerulonephritis. Immune complexes were also found in the glomeruli of these serum-sickness forms of proliferative glomerulonephritis. The concept developed that circulating immune complexes lodged in glomeruli and evoked an inflammatory response. This idea has generally held up in explaining the subendothelial and mesangial immune deposits, the proliferative glomerulonephritis and variable proteinuria in diseases associated with circulating immune complexes, such as lupus erythematosus.

Immune complexes can also be found in the subepithelial region, as in membranous glomerulonephropathy. Proliferation of mesangial cells does not occur, but there is nevertheless marked proteinuria. What determines whether a circulating immune complex settles in the subepithelial versus the subendothelial location? Size and charge of the immune complex are important in this discrimination, in addition to glomerular hemodynamics, glomerular charge and vasoactive

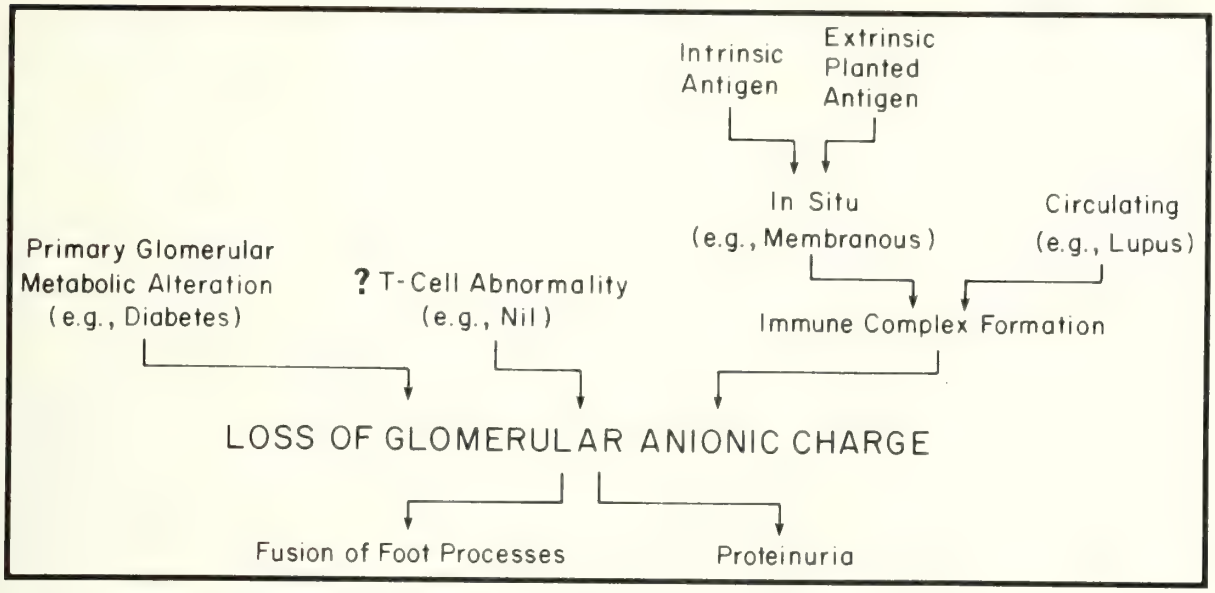

Figure 3.—Pathogenesis and pathophysiology of glomerular proteinuria in nephrotic states.

substances. Couser and Salant[27] have recently questioned whether circulating immune complexes ever come to rest in a subepithelial location and, hence, are ever responsible for the development of membranous glomerulonephropathy. They have based their argument on two principal findings. First, in the experimental serum-sickness models, the circulating immune complexes rest almost exclusively in the subendothelial and mesangial region; there are virtually none found in the subepithelial location except in states of notable antigen excess. Second, in patients with membranous glomerulonephropathy, it is very difficult to find any circulating immune complexes. Couser and Salant have, therefore, put forward an alternative explanation for the derivation of the subepithelial immune complexes demonstrated by immunofluorescence and electron microscopy in biopsy specimens from patients with membranous nephropathy: They are formed in situ. For instance, if there were an intrinsic subepithelial antigen or, alternatively, a circulating antigen were filtered to the subepithelial region and then planted, an antibody might be attracted and an immune complex formed in situ. This subepithelial immune complex could then activate complement, causing diminution in the anionic charge of the glomerular basement membrane with subsequent proteinuria. Couser and colleagues have used the experimental equivalent of membranous glomerulonephritis, called Heymann nephritis, to support their contentions. When an antibody directed against a tubular antigen is perfused into an isolated perfused kidney preparation, immune complexes are found in the subepithelial location, just as is seen in membranous glomerulonephropathy.[28] There are no circulating immune complexes in this model, so that in situ formation of immune complexes must have occurred.

The schematic diagram in Figure 3 is presented to summarize our current understanding of some of the important principles involved in the pathogenesis and pathophysiology of glomerulonephropathies associated with the nephrotic syndrome. The common denominator for the development of proteinuria in a generalized sense and albuminuria in a specific sense, as well as for fusion of epithelial cell foot processes, is the loss of the glomerular anionic charge. This loss of negative charge can be shown histopathologically and physiologically. The loss of the glomerular anionic charge may in turn be due to immune damage ascribed to circulating immune complexes, as in lupus. Alternatively, damage may occur due to in situ immune complex formation, as probably occurs in membranous glomerulonephropathy, due either to an intrinsic subepithelial antigen or to an extrinsic antigen planted in the subepithelial region. Antibody is then attracted to that location, fixes complement and causes in some undefined manner a loss of glomerular anionic charge.

Still another mechanism for glomerular damage is envisioned for nil (or minimal change) disease,

TABLE 1.—*Primary Renal and Systemic Diseases Treatable With Steroids*

	Treatable With Steroids
Renal	
Minimal change (nil)	Yes
Idiopathic membranous	Yes
Membranoproliferative	No
Focal sclerosis	No
Systemic	
Diabetes mellitus	No
Lupus erythematosus	Yes
Amyloidosis	±

in which case no immune complexes can be shown to be present either in the circulation or in the kidney. Shalhoub[29] has postulated that there might be a T-cell abnormality that translates, again in some undefined way, to a loss of glomerular anionic charge. He based his argument on two principal observations: first, the documented association with nil disease of certain T-cell disorders, such as Hodgkin's disease and other lymphomas; second, the clinical observation that there is amelioration of proteinuria in nil disease when the patient contracts measles, a T-cell suppressive state. Finally, metabolic alterations in the glomerular matrix that change the anionic constituents of the glomerular basement membrane, as occurs in diabetes or in amyloidosis, can cause albuminuria.

Treatment

The therapeutic mainstay of nephrotic syndrome is *prednisone,* when a renal biopsy indicates that a patient has an amenable disease. In addition, a *high protein diet* is advocated to compensate for the nitrogen losses due to albuminuria and increased catabolism—that is, to support the requirement for increased hepatic synthesis of albumin. *Diuretic drugs* are useful when there is severe edema but with the important caveat that the plasma volume depletion commonly seen in the nephrotic syndrome is often made worse with diuretic therapy. Injudicious diuretic use can precipitate acute renal failure. *Anticoagulant medications* are indicated when there is evidence of pulmonary embolism or renal vein thrombosis. Finally, as mentioned previously, there is some question whether *antihyperlipidemic drugs* are useful in this syndrome.[4]

The diseases considered treatable with steroids are listed in Table 1. Nil disease continues to be the prototype of the nephrosis that is highly sensitive to steroid treatment. Prednisone usually causes complete amelioration of albuminuria. The collaborative group for the study of the nephrotic syndrome has recently shown that idiopathic membranous nephropathy is also a steroid-responsive disease.[30] In this prospective double-blind study of 72 patients treated with alternate-day, high-dose (125 mg) steroids, a significant reduction in the progression of renal insufficiency, with a tendency toward the regression of albuminuria, was found. This study unfortunately was carried out for only two months so that further studies over a longer period of time will have to be done to confirm these initial very encouraging observations. At UCSF Dr. Hopper and co-workers[31] have shown that women with idiopathic membranous nephropathy have a better prognosis and are more responsive to steroids than men and in another study Hopper and associates[32] have shown that patients with fairly advanced renal insufficiency, even with a glomerular filtration rate of only 20 ml a minute (who would have been excluded from the cooperative study), benefit from steroid therapy. In sum, since minimal change and membranous nephropathy constitute most of the causes of idiopathic nephrotic syndrome in adults, this disease is now considered to be a treatable renal lesion. Unfortunately, membranoproliferative and focal sclerosing glomerulonephropathies are still considered untreatable, as is diabetes mellitus. Lupus, though there is some controversy over the details of therapy, is generally considered to be responsive to steroid or cytotoxic therapy, or both. Finally, amyloidosis may also be treatable when the underlying disease, such as myeloma, is responsive to prednisone.

Finally, a note regarding the interaction of a high protein diet with the use of prednisone in patients who are already azotemic, a not uncommon problematic triad in nitrogen balance confronting the physician treating patients with nephrotic syndrome. The dilemma is the following. When a patient with renal insufficiency and some degree of azotemia is given prednisone, there is a further increase in blood urea nitrogen (BUN) due to steroid-induced hypercatabolism. If a high protein diet is instituted to ameliorate the negative nitrogen balance induced by prednisone, will one only exacerbate the catabolism, making the BUN rise further, and even precipitate the need for dialysis? Based on short-term studies at our institution,[33] the answer to this question is that a high protein (1.3 grams per kg of body weight a

day) and high calorie (30 to 35 kcal per kg a day) diet makes nitrogen balance more favorable (that is, less negative) without further increasing the high urea generation induced by high dose prednisone. The extra dietary protein is, therefore, not additive to the steroid catabolic effect and will not exacerbate the azotemia further, but rather will serve to improve nitrogen balance. Although further long-term studies measuring individual organ function and mass are required, these preliminary studies suggest that increased dietary protein and calorie intake might be useful in patients treated with steroids even when azotemic.

Conclusion

During the past decade, there have been considerable advances in our knowledge of the role of the glomerular wall anionic charge in restricting passage of anionic macromolecules; in our recognition that loss of this anionic charge is inherent in the development of the nephrotic syndrome; in our understanding of the importance of immune complexes formed in situ rather than immune complexes derived from the circulation in causing some forms of the nephrotic syndrome, and finally in our recent substantiation of the efficacy of steroids in treating most adult patients with idiopathic nephrotic syndrome.

REFERENCES

1. Earley LE, Havel RJ, Hopper J Jr, et al: Nephrotic syndrome —Medical Grand Rounds, University of California, San Francisco (Special Conference). Calif Med 1971 Oct; 115:23-41

2. Glassock RJ, Cohen AH, Bennett CH: Primary and secondary glomerular diseases, *In* Brenner BM, Rector FC Jr (Eds): The Kidney, Vol 2, 2nd Ed. Philadelphia, WB Saunders, 1981, pp 1351-1570

3. Glassock RJ: The nephrotic syndrome. Hosp Pract 1979 Nov; 14:105-129

4. Wass VJ, Jarrett RJ, Chilvers C, et al: Does the nephrotic syndrome increase the risk of cardiovascular disease? Lancet 1979 Sep 29; 2(8144):664-667

5. Hopper J Jr, Ryan P, Lee JC, et al: Lipoid nephrosis in 31 adult patients: Renal biopsy study by light, electron, and fluorescence microscopy with experience in treatment. Medicine 1970 Jul; 49:321-341

6. Rosenman RH, Friedman M, Byers SO: The causal role of plasma albumin deficiency in experimental nephrotic hyperlipidemia and hypercholesterolemia. J Clin Invest 1956; 35:522-531

7. Baxter JH, Goodman HC, Allen JC: Effects of infusions of serum albumin on serum lipids and lipoproteins in nephrosis. J Clin Invest 1961; 40:490-498

8. Meltzer JI, Keim HJ, Laragh JH, et al: Nephrotic syndrome: Vasconstriction and hypovolemic types indicated by renin-sodium profiling. Ann Intern Med 1979 Nov; 91(5):688-696

9. Dorhout Mees EJ, Roos JC, Boer P, et al: Observations on edema formation in the nephrotic syndrome in adults with minimal lesions. Am J Med 1979 Sep; 67(3):378-384

10. Landwehr DM, Carvalho JS, Oken DE: Micropuncture studies of the filtration and absorption of albumin by nephrotic rats. Kidney Int 1977 Jan; 11:9-17

11. Brenner BM, Hostetter TH, Humes HD: Molecular basis of proteinuria of glomerular origin. N Engl J Med 1978 Apr 13; 298(15):826-833

12. Brenner BM, Hostetter TH, Humes HD: Glomerular permselectivity: Barrier function based on discrimination of molecular size and charge. Am J Physiol 1978 Jun; 234:F455-F460

13. Bohrer MP, Baylis C, Humes HD, et al: Permselectivity of the glomerular capillary wall—Facilitated filtration of circulating polycations. J Clin Invest 1978 Jan; 61:72-78

14. Bohrer MP, Baylis C, Robertson CR, et al: Mechanisms of the puromycin-induced defects in the transglomerular passage of water and macromolecules. J Clin Invest 1977 Jul; 60(1):152-161

15. Blau EB, Haas JE: Glomerular sialic acid and proteinuria in human renal disease. Lab Invest 1973 Apr; 28:477-481

16. Ryan GB, Karnovsky MJ: An ultrastructural study of the mechanisms of proteinuria in aminonucleoside nephrosis. Kidney Int 1975 Oct; 8(4):219-232

17. Deen WM, Satvat B: Determinants of the glomerular filtration of proteins. Am J Physiol 1981; 241:F162-F170

18. Farquhar MG: The primary glomerular filtration barrier—Basement membrane or epithelial slits? (Editorial). Kidney Int 1975 Oct; 8(4):197-211

19. Venkatachalam MA, Rennke HG: The structural and molecular basis of glomerular filtration. Circ Res 1978 Sep; 43(3): 337-347

20. Latta H, Johnston WH, Stanley TM: Sialoglycoproteins and filtration barriers in the glomerular capillary wall. J Ultrastruc Res 1975 Jun; 51(3):354-376

21. Seiler MW, Venkatachalam MA, Cotran RS: Glomerular epithelium: Structural alterations induced by polycations. Science 1975 Aug; 189(4200):390-393

22. Seiler MW, Rennke HG, Venkatachalam MA, et al: Pathogenesis of polycation-induced alterations (fusion) of glomerular epithelium. Lab Invest 1977 Jan; 36:48-61

23. Robson AM, Giangiacomo J, Kienstra RA, et al: Normal glomerular permeability and its modification by minimal change nephrotic syndrome. J Clin Invest 1974 Nov; 54(5):1190-1199

24. Carrie BJ, Myers BD: Proteinuria and functional characteristics of the glomerular barrier in diabetic nephropathy. Kidney Int 1980 May; 17:669-676

25. Germuth FG Jr: A comparative histologic and immunologic study in rabbits of induced hypersensitivity of the serum sickness type. J Exp Med 1953; 97:257-282

26. Dixon FJ, Vazquez JJ, Weigle WO, et al: Pathogenesis of serum sickness. Arch Pathol 1958; 65:18-28

27. Couser WG, Salant DJ: In situ immune complex formation and glomerular injury. Kidney Int 1980 Jan; 17:1-13

28. Couser WG, Steinmuller DR, Stilmant MM, et al: Experimental glomerulonephritis in the isolated perfused rat kidney. J Clin Invest 1978 Dec; 62(6):1275-1287

29. Shalhoub RJ: Pathogenesis of lipoid nephrosis: A disorder of T-cell function. Lancet 1974 Sep 7; 2(7880):556-560

30. Collaborative Study of the Adult Idiopathic Nephrotic Syndrome: A controlled study of short-term prednisone treatment in adults with membranous nephropathy. N Engl J Med 1979 Dec 13; 301:1301-1306

31. Hopper J Jr, Trew PA, Biava CG: Membranous nephropathy: Its relative benignity in women. Nephron 1982; 29:18-24

32. Hopper J Jr, Biava CG, Tu W-H: Membranous nephropathy: High-dose alternate-day therapy with prednisone. West J Med 1981 Jul; 135:1-8

33. Cogan MG, Sargent JA, Yarbrough SG, et al: Prevention of prednisone-induced negative nitrogen balance. Ann Intern Med 1981; 95:158-161

Important Advances in Clinical Medicine

Epitomes of Progress — Pathology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in pathology that have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Laboratory Tests for Detecting Circulating Immune Complexes

IMMUNE COMPLEXES play a role in the pathogenesis of a variety of diseases, particularly those with signs or symptoms of glomerulonephritis, vasculitis, synovitis, serositis, Raynaud's phenomenon, purpura and even urticaria. The primary approaches used for the diagnosis of immune complex disease in humans have been the identification of immune complexes in tissue specimens of skin, kidney and other organs and serologic analysis of various biological fluids.

Exogenous and endogenous antigens can trigger abnormal immune responses with resulting immune complex disease. Because of the enormous diversity of antigens involved in circulating immune complexes, antigen-specific assays for immune complexes have not found widespread clinical use. However, the antigen-nonspecific techniques have attracted a growing interest. Raji cell assay and C1q-binding assay, both of which involve detection of complement-fixing immune complexes, have been most useful in evaluating immune complex disease.

The Raji cell is a cultured human lymphoblastoid cell line derived from a Burkitt's lymphoma. Raji cell assay is based on the observation that complement-binding immune complexes will bind to cell surface receptor sites for C3b, C3d and C1q. Raji cells are normally devoid of membrane-bound immunoglobulin and the technique quantitates immune complexes bound to the cell by measuring the uptake of radioactive antibody to immunoglobulin G in the complexes. The assay is carried out at 37°C to minimize false-positive results that may be possible with rare, warm-acting types of antilymphocytic antibodies.

The sera to be tested in the Raji cell assay should be fresh or stored at −70°C and not subjected to repeated freezing and thawing. The sensitivity of the assay is about 6 μg of aggregated human globulin (AHG) per ml of serum. Studies have shown that in only 3 percent of normal subjects do values of AHG exceed 12 μg per ml of serum. In patients with autoimmune, infectious and malignant diseases, 42 percent to 97 percent were found to have positive findings on testing for immune complexes. High concentrations of Raji cell-bound IgG in the form of immune complexes were found in patients with autoimmune diseases with a mean of 100 to 300 μg of AHG

per ml. Intermediate concentrations of immune complexes were found in patients with infective bacterial endocarditis, viral diseases and malignant tumors, with a mean of 50 to 100 μg of AHG equivalent per ml. In follow-up studies, a good correlation was observed between concentrations of immune complexes and disease activity in patients with autoimmune disorders, infectious diseases and malignancy.

The major disadvantages of the Raji cell technique are the possibility of false-positive results due to the presence of warm, reactive antilymphocytic type of IgG antibodies and interaction of antibodies in serum with cytoplasmic or nuclear antigen liberated from dead cells. The warm reactive IgG antilymphocytic antibodies are often present in extremely small amount, are of low affinity and react poorly with Raji cells under the conditions of the assay. In addition, the assay is carried out at 37°C to minimize the effects of the antilymphocyte antibodies.

The C1q-binding assay measures the ability of circulating immune complexes to bind purified, radiolabeled C1q, the first component of complement. If such immune complexes are present, they will bind the C1q, which will then be precipitated by polyethylene glycol (PEG). Free C1q is not precipitable by PEG. The percentage of the total added C1q that is precipitated is calculated and expressed as "percent bound." Normal ranges are determined in each laboratory and typical results are as follows: 0 percent to 13 percent bound = normal, 13 percent to 16 percent bound = borderline and greater than 16 percent = abnormal.

Certain cryoglobulins, cold agglutinins and rheumatoid factors may be responsible for positive results even though they may not be an integral component of a serum immune complex. C1q also binds to heparin, protamine, lipopolysaccharide, C-reactive protein, DNA and phosphoryl choline.

The Raji cell and the C1q-binding assays measure different properties of immune complexes: the former measures the presence of C3 already bound and so activated that the entire complex can bind to the Raji cell C3 receptor; the latter measures the presence of free binding sites available to bind C1q. Frequently results of the two assays will be discordant, indicating the value of doing both tests in determining the presence of circulating immune complexes.

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REFERENCES

Lambert PH, Dixon FJ, Zubler RH, et al: A WHO collaborative study for the evaluation of eighteen methods for detecting immune complexes in serum. J Clin Lab Immunol 1978; 1:1-15

Theofilopoulos AN, Pereira AB, Eisenberg RA, et al: Assays for detection of complement-fixing immune complexes (Raji cell, conglutinin, and anti-C3 assay), chap 22, *In* Rose NR, Friedman H (Eds): Manual of Clinical Immunology. Washington DC, American Society for Microbiology, 1980, pp 186-192

Zubler RH, Nydegger U, Perrin LH, et al: Circulating and intra-articular immune complexes in patients with rheumatoid arthritis—Correlation of ^{125}I-C1q binding activity with clinical and biological features of the disease. J Clin Invest 1976 May; 57:1308-1319

Herpes Simplex Virus Infections

HERPES SIMPLEX INFECTIONS are caused by a double-stranded DNA virus that measures 100 to 140 nm in diameter. Two antigenic types of herpes simplex virus (HSV) can be distinguished. HSV type 1 causes mainly lesions of the oral mucous membranes and skin lesions above the waist. HSV type 2 affects primarily the genital tract and is usually isolated from lesions below the waist.

Humans are the only known reservoir of HSV and this virus can be isolated from 2 percent to 5 percent of healthy persons. The virus is usually transmitted by direct contact—that is, hand to mouth, kissing, sexual contact and so forth—and has an incubation period that lasts from 3 to 12 days.

Primary infections are common between the first and fifth years of life and by the age of 40 70 percent to 90 percent of persons carry HSV antibodies. However, clinical disease will develop in only 1 percent of susceptible hosts, while the other 99 percent of the infections are asymptomatic. Recurrent infections are common, occurring in 15 percent to 40 percent of patients, and are usually triggered by excitants such as fever, allergy, menstruation and mechanical or psychological trauma. Herpes encephalitis is a serious complication produced by this virus and is the most common cause of fatal sporadic encephalitis in the United States.

Neonatal herpes may be acquired during the intrauterine or perinatal period and affects approximately one infant in 8,000 deliveries. The greatest risk occurs perinatally as the result of exposure to an infected birth canal. Pregnant women with herpes genitalis should be carefully monitored and delivered by cesarean section if there is any possibility that the virus may infect the baby during the vaginal delivery.

Both type 1 and type 2 HSV have been incriminated as possible causal agents in human cancer. So far, however, no definitive evidence is available but a correlation does appear between squamous

cell carcinoma of the cervix and infection with HSV type 2.

Numerous drugs including vidarabine (adenine arabinoside), idoxuridine, ribavirin, acyclovir and interferon have been used for the treatment of HSV infections. Although some positive results have been obtained there is a great need for more investigation in the area of antiviral chemotherapy for HSV.

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REFERENCES

Nahmias AJ, Dowdle WR, Schinazi RF: The Human Herpesviruses—An Interdisciplinary Perspective. New York, Elsevier, 1981

Saral R, Burns WH, Laskin OL, et al: Acyclovir prophylaxis of herpes-simplex-virus infections. N Engl J Med 1981 Jul 9; 305:63-67

Current Problems With Parasites

IN RECENT YEARS refugees and immigrants have brought many parasitic infections into the Western United States. People arrive from Asia with liver fluke infection, paragonimiasis and hookworm, as well as falciparum malaria. Drug-resistant strains of malaria occur in Asia and in other parts of the world and are brought into the United States by refugees and by US citizens traveling abroad.

One may find giardiasis, intestinal amebiasis or amebic liver abscess in persons without a history of foreign travel, while other intestinal infections such as ascariasis and trichuriasis are more commonly seen in recent immigrants. Although light infections with *Trichuris* and hookworm are often of little clinical importance, infection with *Taenia solium* is of great concern because it exposes patients and people around them to cysticercosis. In recent years central nervous system cysticercosis has been seen in patients who have acquired the infections locally.

The prevalence of giardiasis and amebiasis is much higher in homosexuals than in heterosexuals. This has now been well documented. Because of frequent reinfection, homosexuals more commonly receive antiparasitic drug therapy. It is important to realize that some of these drugs may be mutagenic and indiscriminate use may pose a real hazard to patients.

Recent reports of the occurrence of *Pneumocystis carinii* pneumonia in homosexuals are also of concern. Cytomegalovirus (CMV) was present in several of these individuals and may have resulted in some degree of impaired immunity. Fatal disseminated parasitic disease often develops in immunosuppressed patients. Most common in these individuals are toxoplasmosis, pneumocystosis and strongyloidiasis. However, amebiasis and other (inapparent) low-grade infections may also disseminate in patients with an impaired immune system, whether drug-induced, a result of poor nutrition, or concomitant infection.

Careful examination for intestinal parasites *before* administration of immunosuppressive therapy is essential. Not all clinical laboratories do this adequately. Stool specimens fixed in polyvinyl alcohol (PVA) immediately after passage can be sent to reference laboratories recommended by local public health authorities. The essential permanent stain can be prepared from material fixed in PVA by patients at home or by a ward nurse. State public health laboratories and the Centers for Disease Control, Atlanta, will advise on the availability of serologic tests for parasitic diseases. Certain commercially available kits for serologic testing may yield results of dubious value. Many are now being evaluated for reliability. When in doubt, a physician should check the accuracy of specific tests with the above agencies.

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REFERENCES

Garcia LS, Voge M: Diagnostic clinical parasitology: I. Proper specimen collection and processing. Am J Med Technol 1980 Jun; 46(6):459-466

Hoffman SL, Barrett-Connor E, Norcross W, et al: Intestinal parasites in Indochinese immigrants. Am J Trop Med Hyg 1981 Mar; 30(2):340-343

Jung RC, Rodriguez MA, Beaver PC, et al: Racemose cysticercus in human brain—A case report. Am J Trop Med Hyg 1981 May; 30(3):620-624

William DC, Shookhoff HB, Felman YM, et al: High rates of enteric protozoal infections in selected homosexual men attending a venereal disease clinic. Sex Transm Dis 1978 Oct-Dec; 5:155-157

Therapeutic Drug Monitoring

THE RECOGNIZED medical usefulness of the measurement of drug levels in patients produced a considerably increased demand for such monitoring during the 1970's. This specialty area continues to grow rapidly. Clinicians in both small and large medical centers have come to expect and to depend on laboratory determinations to monitor the course of acute or chronic drug therapy.

Drugs commonly monitored include those used in cardiology (digoxin, quinidine, procainamide hydrochloride and lidocaine hydrochloride), neurology (phenobarbital, phenytoin, primidone, carbamazepine and valproic acid), psychiatry (amitriptyline hydrochloride, nortriptyline hydrochloride and lithium), pulmonary medicine (theophylline), oncology (methotrexate and cisplatin) and infectious diseases (gentamicin and tobramycin). The purpose of a drug assay may be to assure

patient compliance with the therapeutic regimen, to achieve a pharmacologically effective drug concentration in serum or to prevent potentially toxic drug accumulation in the body.

For routine therapeutic monitoring purposes, a drug assay need not be highly specific for the unchanged drug in serum as long as the result is quantitatively accurate and can be correlated with clinical response. For instance, there are some relatively unsophisticated laboratory procedures still in use for drugs such as phenobarbital, phenytoin, quinidine and theophylline that involve spectrophotometry.

More recently, however, a subspecialty of pharmacology known as pharmacokinetics has been applied to the interpretation of patients' drug levels. The rate of elimination of a drug, its volume of distribution and suggested changes in dosage or dosing interval can be accurately predicted using pharmacokinetic calculations. For these applications, the laboratory assay should be sensitive to small concentrations of the drug, highly quantitative and capable of measuring individually the unchanged drug and its active metabolites. Simple to perform but very specific immunoassays are now commercially available for many of the commonly monitored drugs. The most successful therapeutic drug monitoring programs in hospital settings involve a cooperative effort between clinicians, laboratory personnel and clinical pharmacists.

RANDALL C. BASELT, PhD

REFERENCES

Baselt RC: Analytical Procedures for Therapeutic Drug Monitoring and Emergency Toxicology. Davis, CA, Biomedical Publications, 1980

Kalman SM, Clark DR: Drug Assay: The Strategy of Therapeutic Drug Monitoring. New York, Masson Publications, 1979

Sadee W, Beelen GCM: Drug Level Monitoring. New York, John Wiley & Sons, 1980

Immunohistochemistry in Modern Pathology

IMMUNOHISTOCHEMISTRY has revolutionized pathology by allowing ready recognition of tissue antigens not identifiable by either routine light or electron microscopy. Immunohistochemistry is a general term describing the techniques used to stain tissue antigens through the use of antibodies. Immunofluorescence and immunoperoxidase are the two main forms of immunohistochemistry. As the first step, each method requires an antibody, the so-called primary antibody, that is directed against the antigen whose presence or absence in a given tissue one wishes to determine. The primary antibody must be labeled with a tag such as fluorescein or horseradish peroxidase. The fluorescein tag is seen with the use of a fluorescence microscope and positive staining appears as a bright light against a dark background. The horseradish peroxidase tag acts on a soluble chromogenic substrate to form an insoluble colored precipitate that is examined with an ordinary light microscope. Although immunofluorescence is advantageous for certain purposes, such as the staining of antigens seen solely in cell membranes, it requires frozen tissue and a fluorescence microscope and does not permit recognition of much histologic detail in the nonfluorescing background area of the tissue. The immunoperoxidase technique, however, can be done on routinely processed formaldehyde-fixed paraffin-embedded tissue. The method does not require a special microscope and the tissue can be counterstained with hematoxylin to allow recognition of fine histologic detail.

The first major diagnostic use of immunohistochemistry was in the classification of the various forms of glomerulonephritis. Immunoglobulins, complement and other serum proteins can be precisely located in the glomeruli with immunofluorescent techniques. Unlike purely morphologic techniques such as electron microscopy, immunofluorescence is able to distinguish among immunoglobulin subclasses and the various components of the complement pathway, thus permitting a more precise diagnosis and insight into the pathogenesis of the disease.

Today immunohistochemistry has become an aid in many of the problems facing surgical pathologists. Some lymphomas can be differentiated from nonlymphoid neoplasms because many neoplastic lymphoid cells produce immunoglobulins that are expressed in the cytoplasm or on the membranes of the malignant cells. The often troublesome distinction between reactive lymphoid hyperplasia and lymphoma is also aided by immunohistochemistry. The demonstration of a polyclonal proliferation of both k- and λ-light chains containing B cells is characteristic of reactive lesions, whereas B-cell lymphomas generally stain monoclonally for only one class of immunoglobulin light chain. The arrival of antibodies specific for T lymphocytes promises to help in the differentiation of B-cell from T-cell lymphomas.

Immunohistochemistry can establish the cell lineage and site of origin of undifferentiated or metastatic neoplasms. Factor VIII, for example, is

a coagulation factor produced by endothelial cells and therefore is helpful in the diagnosis of angiosarcoma. Prostatic acid phosphatase is an isoenzyme present only in prostatic adenocarcinomas and enables a pathologist to differentiate between a primary pulmonary adenocarcinoma and a single nodule of metastatic prostatic carcinoma. Such distinctions are obviously clinically and therapeutically important. In the future, antibodies specific for tumors from all sites of the body will probably become available as organ-specific antigens are discovered against which corresponding antibodies can be produced. The rapidly expanding technology of monoclonal antibody production promises to yield large quantities of relatively inexpensive, commercially available and standardized antisera.

Immunohistochemistry has become an indispensable diagnostic aid in the modern anatomic pathology laboratory because it permits the identification of tissue antigens not recognizable by either routine light or electron microscopy. Diverse structures ranging from the tiny monoamines and polypeptide hormones of the nervous system, the amine precursor uptake and decarboxylation (APUD) cell system and the pituitary gland to complex infectious organisms such as viruses and bacteria are all recognizable through the use of immunohistochemistry.

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REFERENCES

Sternberger LA: Immunocytochemistry, 2nd Ed. New York, John Wiley & Sons, 1979

Taylor CR: Immunoperoxidase techniques: Practical and theoretical aspects. Arch Pathol Lab Med 1978 Mar; 102:113-121

Steroid Hormone Receptors in Histologic Diagnosis

TISSUE HORMONE receptor assays are used most often as additional guides in the treatment of breast carcinoma. Estrogen receptor is usually assayed by direct assessment of the estrogen-binding activity of cytosols prepared from tumor tissue (dextran-coated charcoal and sucrose gradient centrifugation techniques). The presence of high-affinity binding sites according to these methods is accepted as a reliable indicator of the probable response of tumor to hormonal manipulation. Progesterone receptor activity is assessed by similar techniques.

These methods have certain disadvantages including high cost, prolonged turnaround and the need for fresh unfixed tissues at the time of biopsy or major surgical procedure. A more important problem relates to tissue sampling—that is, just how much of the tissue block from which the cytosol is prepared consists of breast carcinoma cells and just how much is stroma, myoepithelium or connective tissue. Thus there is a potentially large unknown and unknowable variable in all cytosol assays.

Immunohistologic methods for identifying estrogen receptor in tissue sections seek to avoid these disadvantages. Some investigators have used immunofluorescence methods in an attempt to locate estrogen receptor in frozen sections of breast cancer. In one method estradiol (in the form of polymerized estradiol phosphate [PEP]) is added to the frozen section of breast cancer, followed by specific antibody against estradiol. In principle the PEP binds to free estrogen receptor in the tissue and the antiestradiol antibody then identifies the sites of PEP binding (at the presumed receptor sites). Finally, the location of the antiestradiol antibody is then revealed by immunofluorescence methods.

Immunoperoxidase techniques are similar in principle to the immunofluorescence method, except that fixed paraffin sections of breast tissue are used. This has the dual advantage of providing better morphologic detail while avoiding the need to collect frozen material at the time of biopsy. Initial immunoperoxidase studies used pretreatment with PEP as in the immunofluorescence method. However, it has since been proposed that the addition of antiestradiol antibody alone, without the preceding PEP, may detect estrogen bound in vivo to functionally active receptor sites in breast cancer cells. A still more recent variation of the immunoperoxidase method attempts to use antibodies prepared against the receptor protein itself. Monoclonal antibodies with activity against the presumed estrogen protein have been found successful in immunostaining of paraffin sections (M. Nadji, MD, University of Miami, personal communication, October 1981).

A number of correlations have been established between immunofluorescence methods, immunoperoxidase methods and orthodox cytosol assays for estrogen receptor, but at this time there is no direct proof that the immunohistologic methods are measuring the same high-affinity receptor protein that is detected by the cytosol assays. The ultimate assessment of clinical application of these immunohistologic methods rests in the performance of clinical trials, comparing the results of hormonal manipulation with the pattern of im-

munostaining for receptor. For those methods that are applicable to formaldehyde-paraffin sections, such studies can be performed retrospectively on materials stored as paraffin blocks. That immunostaining of tissue sections for estrogen receptor is rapid, relatively inexpensive, may be applicable to fixed-paraffin tissues and avoids the sampling problems inherent in cytosol assays is motivation enough to ensure that these studies of possible clinicopathologic correlations are pursued actively.

CLIVE R. TAYLOR, MD

REFERENCES

Chamness GC, Mercer WD, McGuire WL: Are histochemical methods for estrogen receptor valid? J Histochem Cytochem 1980 Aug; 28:792-798

Mercer WD, Lippman ME, Wahl TM, et al: The use of immunocytochemical techniques for the detection of steroid hormones in breast cancer cells. Cancer 1980 Dec 15; 46:2859-2868

Taylor CR, Cooper CL, Kurman RJ, et al: Detection of estrogen receptor in breast and endometrial carcinoma by the immunoperoxidase technique. Cancer 1981 Jun 1; 47(11):2634-2640

Walker RA, Cove DH, Howell A: Histological detection of oestrogen receptor in human breast carcinomas. Lancet 1980 Jan 26; 1(8161):171-173

Evaluation of Hypoglycemia

ASYMPTOMATIC HYPOGLYCEMIA has been observed frequently enough in control populations of women (17 percent) and men (25 percent) during a five-hour oral glucose tolerance test (OGTT) to be considered a variant of normality. Reactive hypoglycemia—that is, the symptoms of weakness, shakiness, sweating, tremor and tachycardia—may occur two to five hours after a glucose load as the plasma glucose falls below 50 mg per dl, especially in patients who have had gastrointestinal operations or have early diabetes mellitus. These symptoms are due to the adrenergic discharge triggered by the fall in plasma glucose and not the specific level or nadir observed. No clear-cut lower limit of normal plasma glucose values allows the diagnosis of hypoglycemia on the basis of OGTT results alone. These symptoms are often the result of other causes, such as anxiety, hyperthyroidism, pheochromocytoma or insulinoma.

If a patient's symptoms are to be attributed to hypoglycemia, it is important to determine whether they occur in the fasting state or after eating a meal, and not after a glucose load. OGTT is inappropriate for the diagnosis of fasting hypoglycemia, which is generally due to serious organic disease. To document fasting hypoglycemia, a 48- to 72-hour period of fasting should be supervised in the hospital or until hypoglycemia symptoms occur. At this time serum glucose, insulin and C-peptide levels should be determined. If the serum insulin is greater than 6 μU per ml when serum glucose is less than 40 mg per dl, then an insulinoma is most likely. The normal ratio of glucose to insulin should be greater than 3.6. Patients with insulinoma usually have a ratio of less than 2.5. If the serum C-peptide level is low, however, in relation to the serum insulin, then the patient may be taking insulin surreptitiously. If a patient's symptoms are occurring after meals, a meal tolerance test (a standard breakfast after fasting 10 to 16 hours) should be done. Blood samples are taken every half hour for five hours after the meal. If the lowest glucose value exceeds 60 mg per dl, the result is normal. If the value is less than 50 mg per dl, the tolerance test result is abnormal.

Some individuals may have symptoms during the tolerance test, yet the glucose values are normal. It is important to correlate the onset of clinical symptoms with the glucose values observed during the meal tolerance test. Thus it is possible some other factors such as glucagon or gastrointestinal disorders are altered and trigger the symptoms.

RUSSELL J. EILERS, MD

REFERENCES

Fariss BL: Prevalence of post-glucose-load glycosuria and hypoglycemia in a group of healthy young men. Diabetes 1974 Mar; 23:189-191

Johnson DD, Dorr KE, Swenson WM, et al: Reactive hypoglycemia. JAMA 1980 Mar 21; 243(11):1151-1155

Jung Y, Khurana RC, Corredor DG, et al: Reactive hypoglycemia in women—Results of a health survey. Diabetes 1971 Jun; 20:428-434

Watts NB: Oral glucose tolerance test may be done too fast. Lab World 1981 Jun; 32:68-72

Hair Analysis: A Potential Diagnostic Tool

HAIR CAN BE easily collected from a donor, stored without deterioration and analyzed with great sensitivity with recently developed technologies. Trace elements accumulate at concentrations at least ten times higher than those in blood or urine and may provide a continuous record of nutritional status, exposure to drugs or exposure to pollutants in the environment such as the heavy metals lead and mercury.

The elements and drugs found in hair are incorporated during synthesis of filaments in the follicle. Apparently the disulphide bonds in the cuticular protein of hair are sites for the deposition of metal during hair formation. These bonds are also interaction sites for exogenous metals from air, water, sweat or grooming materials. As the follicles are exposed to more substances

over time, the amount of substances incorporated in hair filament changes. Thus sequential analysis of filaments, from follicles to tip, provides a timed record of exposure. The intrinsic elements are of medical interest. The extrinsic elements resulting from environmental contaminations interfere with the interpretation of results if one is seeking the low values of nutritional studies, in contrast to the high values of toxicology.

The key to interpretation is the site of collection of the sample on the body and how it is cleaned or prepared before analysis. For example, 5-cm long maternal hair strands measured from the scalp correspond to a fetal growth period from two weeks before conception through 16 to 19 weeks of gestation. The concentration of metals detected in this hair indicates fetal exposure to those metals during the first 16 to 19 weeks of gestation. The results will be accurate providing the laboratory has standardized any one of 24 possible preanalysis methods for cleaning the hair to remove extrinsic metal contamination from intrinsic elements.

Analysis of human hair is an experimental technology that has clinical promise. Currently, valid tests are available to confirm heavy metal toxicity due to lead, mercury and arsenic exposure.

RUSSELL J. EILERS, MD

REFERENCES

Chittleborough GA: A chemist's view of the analysis of human hair for trace elements. Sci Total Environ 1980 Jan; 14:53-75

Klevay LM: Hair as a biopsy material: Progress and prospects. Arch Intern Med 1978 Jul; 138:1127-1128

Maugh TH II: Hair: A diagnostic tool to complement blood serum and urine (News). Science 1978 Dec; 202(4374):1271-1273

The Role of *Chlamydia* in Sexually Transmitted Diseases

THE BROAD SPECTRUM of clinical infections due to *Chlamydia trachomatis* has become apparent only in recent years. In the United States it is estimated that approximately 3 million new cases of chlamydial infections occur each year so that it may be the most frequent sexually transmitted disease in this country.

C trachomatis was identified in 40 percent to 50 percent of men with nongonococcal urethritis. A presumptive diagnosis of chlamydial infection can be made in these patients by excluding gonorrhea with a Gram stain and culture. *C trachomatis* was also found to be a common cause of epididymitis in men under 35 years of age.

In women *Chlamydia* can be isolated from 80 percent to 90 percent of patients with hypertrophic cervical erosions or with endocervical mucopurulent discharge. In addition, *C trachomatis* was recovered in 30 percent to 40 percent of patients with pelvic inflammatory disease.

Recently *C trachomatis* has been found in 30 percent of infants admitted to the hospital with a diagnosis of interstitial pneumonia. Furthermore, neonatal inclusion conjunctivitis may be the most common eye disease of newborns in the United States. Infants probably acquire these infections during delivery, though the possibility of prenatal or postnatal infection has not been completely excluded.

Chlamydial diagnostic services are now available in several centers and therapy with a wide variety of antimicrobial drugs, including erythromycin, tetracycline or sulfonamides, is highly effective. An increased awareness by the medical community is required in order to effectively control this pathogen.

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REFERENCES

Schachter J: Chlamydial infections (Parts 1-3). N Engl J Med 1978 Feb 23, Mar 2, Mar 9; 298:428-435, 490-495, 540-549

Taylor-Robinson D, Thomas BJ: The role of *Chlamydia trachomatis* in genital-tract and associated diseases. J Clin Pathol 1980 Mar; 33:205-233

HLA and Paternity Testing

UNTIL RECENTLY the results of blood group testing for the determination of paternity were admissible as legal evidence only for the exclusion of a putative father. Because of the extreme diversity and low frequency of occurrence of different human leukocyte antigens (HLA) in the population, it is now possible to calculate with a very high degree of certainty the likelihood of a nonexcluded male being the actual father. Fourteen states now accept the results of these studies as legal evidence of paternity. In reporting the effects of HLA testing in 1,000 cases in which paternity was not excluded by ABO blood group testing, Terasaki noted that in 25 percent of the cases paternity could be excluded by HLA testing. Of the remaining cases 67 percent had a probability of paternity of over 95 percent and 16 percent of the cases had a probability of paternity over 99 percent. In this regard the HLA system is so discriminating that it has been possible to relate the paternity of a dizygotic twin pair to two different fathers.

The genes that control the inheritance of HLA are located on the short arm of human chromosome 6. Because everyone possesses a maternally inherited and a paternally inherited sixth chromo-

some, the identification of the HLA type is the first step towards the indirect identification of that person's sixth chromosome. If the HLA of the parents of that individual are known, it is generally easy to determine which HLA are derived from the maternal chromosome and which HLA are derived from the paternal chromosome. It therefore follows that if a child possesses no HLA in common with an alleged father, that man is excluded. But if certain HLA patterns are common to both the child and the alleged father the statistical likelihood of that man being the father can be determined. This statistic is influenced by how frequently the HLA patterns being shared are found in the general population. Because there are many HLA patterns, any single pattern tends to occur rarely and often a probability of paternity of 95 percent or greater is found. Despite this, we and others have experienced rare situations in which an alleged father could not be excluded by HLA testing but was successfully excluded by red-cell antigen inheritance patterns or isoenzymes. We therefore recommend that, in addition to HLA testing, as many erythrocyte and serum markers as possible be analyzed in the evaluation of possible paternity.

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REFERENCES

Terasaki PI: Resolution by HLA testing of 1,000 paternity cases not excluded by ABO testing. J Family Law 1978; 16:543-557

Terasaki PI, Gjertson D, Bernoco D, et al: Twins with two different fathers identified by HLA. N Engl J Med 1978 Sep 14; 299(11):590-592

Clinical Application of Free Cortisol Estimation

FROM TIME TO TIME the evaluation of a hypertensive patient raises the question of adrenal hyperfunction.

Excess adrenal corticosteroid secretion, Cushing's syndrome, is associated with truncal obesity, a florid appearance and hypertension. Many middle-aged obese individuals with no evidence of hormonal imbalance have a similar appearance. The laboratory can provide useful information to distinguish the two groups.

Cortisol is the major glucocorticoid secreted by the adrenal cortex in response to adrenocorticotropic hormone (ACTH) stimulation. About 90 percent of it is carried in the blood bound largely to an α-globulin called transcortin. The remainder occurs as physiologically active free cortisol. Bound cortisol acts as a reservoir for a supply of hormone available to the tissues of the body. Free cortisol is integrated into body metabolism and approximately 1 percent of it is secreted unaltered in the urine.

Plasma cortisol is a direct measure of bound plus unbound hormone. Diurnal variation normally occurs, with morning awakening levels approximately twice the 4 to 5 PM values. Because elevations of transcortin are associated with increased levels of cortisol, one anticipates elevated plasma cortisol in association with pregnancy or use of agents such as birth control medication.

Urinary free cortisol levels reflect the biologically active unbound hormone. The level is only loosely related to 17-hydroxycorticoids or 17-ketogenics, which are largely liver-derived metabolic breakdown products of cortisol. These derivatives vary with liver function, drugs affecting liver functions and cortisol levels. Excretion of 17-hydroxycorticoid varies with body size and thyroid status.

Urinary free cortisol does not have such interferences. It is one of the most reliable, informative tests to differentiate patients with endogenous Cushing's syndrome from normal persons or from those with central obesity, hirsutism and abdominal striae. Because the test is a specific radioimmunoassay there is no technical interference from drugs. The 24-hour urine sample averages out diurnal variations. Urinary free cortisol normal values are 20 to 100 μg per 24 hours.

An abnormally elevated test result should be followed by plasma cortisol estimations with dexamethasone suppression to clarify the comparative importance of the pituitary and adrenal glands in a patient's illness. The test is not useful for evaluating adrenal insufficiency.

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REFERENCES

Eddy RL, Jones AL, Gilliland PF, et al: Cushing's syndrome: A prospective study of diagnostic methods. Am J Med 1973 Nov; 55:621-630

Zadik Z, De Lacerda L, De Carmargo LAH, et al: A comparative study of urinary 17-hydroxycorticosteroids, urinary free cortisol, and the integrated concentration of plasma cortisol. J Clin Endocrinol Metab 1980 Nov; 51(5):1099-1101

Hemapheresis

WITH THE ADVENT of modern technology, therapeutic bloodletting has attained a new aura of respectability. *Hemapheresis,* a term derived from the Greek word *aphairesis,* meaning "taking away," refers to procedures in which a component from donor or patient blood is selectively removed

and the remainder of the blood returned to the person.

The major improvement of the new technology has been in allowing selectivity of the component removed, and more specific terms such as plasmapheresis, leukapheresis and plateletpheresis reflect this selective removal.

The collection, component removal and return of the blood are performed by manual and semiautomated techniques, many of these involving differential centrifugation. These methods have greatly enhanced our ability to provide blood component support of platelets and granulocytes for patients undergoing aggressive chemotherapy.

Hemapheresis has also been used more directly on patients to treat a number of diseases, particularly those in which an abnormal protein, an autoimmune antibody or an antigen-antibody complex may play a role. However, only in the hyperviscosity syndrome is there broad agreement that this is the treatment of choice. Promising results have been seen in Goodpasture's syndrome and myasthenia gravis, but the actual contribution of plasmapheresis, drug therapy and supportive care have not yet been defined. In thrombotic thrombocytopenic purpura, the number of patients reported to survive seems to be increasing but, here again, the relative roles of supportive care, earlier diagnosis, drug therapy and plasmapheresis are unclear.

The use of plasmapheresis in the treatment of other conditions is even further from clear proof of efficacy. Recently the National Center for Health Care Technology reported on its evaluation of plasmapheresis in the treatment of rheumatoid arthritis. The report concluded that "plasmapheresis, lymphoplasmapheresis and lymphapheresis for rheumatoid arthritis should be considered experimental, with the possible exception of treatment for life-threatening complications of rheumatoid arthritis such as vasculitis, cryoglobulinemia or hyperviscosity syndrome."

So despite the continuing interest in possible applications of hemapheresis, many of the current applications must still be considered experimental. Most of the successful reports of therapeutic hemapheresis have involved only small numbers of patients.

Careful consideration of what therapeutic goals are desired and how to objectively assess their achievement is most important. These procedures are expensive and not innocuous. Fatal myocardial infarction has been reported to occur during hemapheresis, though no definite causal relation has been established. Increased risk of sepsis in immunosuppressed patients, rebound paradoxical increase in unwanted antibodies and anticoagulant-related citrate toxicity are some of the complications to be considered. The as-yet-unproved benefits of hemapheresis must be weighed against the potential and as-yet-uninvestigated, long-term and short-term ill effects, as well as the substantial health care costs.

HAROLD S. KAPLAN, MD

REFERENCES

Apheresis in the Treatment of Rheumatoid Arthritis. Assessment Report Series, Vol 1, No. 6. Rockville, MD, National Center for Health Care Technology, 1981

Valbonesi M, Garelli S, Mosconi L, et al: Plasma exchange in the management of selected neurological diseases. Plasma Therapy 1981; 2:13-18

Waldenström JG: Plasmapheresis—Bloodletting revived and refined. Acta Med Scand 1980; 208:1-4

Wysenbeek AJ, Smith JW, Krakauer RS: Plasmapheresis II: Review of clinical experience. Plasma Therapy 1981; 2:61-71

Value of the Muscle Biopsy

THE MAJOR REASON for doing a muscle biopsy is to elicit and confirm the presence of neuromuscular disease. In the past pathologists have been confined to evaluating the presence of denervation, myopathy or inflammation. With the advent of histochemistry, electron microscopy, immunohistochemistry and specialized biochemical procedures, pathologists are now able to evaluate neuromuscular disease from a broader perspective.

Physicians responsible for the clinical evaluation and care of patients with neuromuscular disorders must be in close communication with the pathologist before and after the biopsy. For optimal results a skilled surgeon interested in neuromuscular disorders should do the procedure.

To obtain maximum information, biopsy specimens must be properly processed, with portions soaked in isopentane cooled by liquid nitrogen for histochemistry, another portion processed for electron microscopy and fresh or frozen material stored for later detailed microchemistry, if needed. Such sophisticated procedures, equipment and interpretive expertise for the coordinated investigation of neuromuscular disease preclude routine evaluation of biopsy specimens in most community hospitals. However, we have found that with communication between the referring hospital staff and personal transport of a biopsy specimen (without freezing) within a half hour, excellent preservation can be obtained for histochemical and biochemical results.

Biopsy specimens undergo an enzyme histo-

chemical profile for defining fiber types. Type I fibers are characterized by relatively high mitochondrial oxidative enzyme activity in contrast to type II fibers, which rely more on glycogen as an energy substrate. Morphometric analysis of preferential change in fiber types permits recognition of diseases selective for specific fiber types. Such analysis is useful in determining congenital fiber-type disproportion (CFTD) or fiber-type grouping typical of reinnervation. Abnormal aggregations of mitochondria are typical of the "ragged red" neuromyopathies and other mitochondrial myopathies. Abnormal activity of the lysosome system identified by acid phosphatase deposition in fibers is characteristic of chloroquine myopathies and acid maltase deficiency (Pompe's disease). Histochemical semiquantitative estimation of enzyme activity may be of help in defining enzyme deficiencies such as myophosphorylase and phosphofructokinase deficiencies, both associated with abnormal ischemic forearm tests.

Electron microscopy is expensive and often unrewarding. Ultrastructural examination should be reserved for selected muscle specimens in which histochemical abnormalities have been identified. Abnormal reactions primarily affecting myofilaments with the formation of ring fibers and target fibers, abnormalities of the transverse Z band with the formation of nemaline inclusions (nemaline myopathy) and confirmation of abnormal mitochondria in the mitochondrial myopathies are typical examples. Unusual organelles including tubular aggregates, masses of myeloid bodies and fingerprint inclusion bodies add specificity to the classification of muscular disease.

Direct immunofluorescence has been applied to the evaluation of muscle disease. Vascular, fiber, perimysial and sarcolemma-basement membrane depositions of immunoglobulins have been identified in patients with connective tissue disorders. Often, to evaluate for the presence of selected neuromyopathies, biochemical analysis is required. For instance, a case of atypical central core disease was found to have a specific deficiency of fructose 1,6-diphosphatase. Another unusual case concerned a 60-year-old woman in excellent health in whom acute cramping and myoglobinuria suddenly developed after heavy exertion and who was found to lack myophosphorylase (McArdle's disease). Recently, electrophoretic techniques have disclosed some genetic heterogeneity of myophosphorylase deficiency in which some patients were found to lack the enzyme activity but retained the enzyme protein. Our case underwent sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis, which revealed the absence of the myophosphorylase band corresponding to that group lacking both enzyme and protein moieties. The evaluation of long-standing cramps with or without muscle weakness occasionally reveals increased intrafiber lipid. In such cases a biopsy specimen must be analyzed for carnitine and appropriate carnitine transferase activities.

In summary, the application of recent technologies provide a greater understanding of the evolution, natural history and pathogenesis of human neuromuscular disease. The minor discomfort of the technical procedure is greatly overshadowed by the wealth of diagnostic and prognostic information forthcoming from more refined analysis.

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REFERENCES

Kar NC, Pearson CM, Verity MA: Muscle fructose 1,6-diphosphatase deficiency associated with an atypical central core disease. J Neurol Sci 1980 Nov; 48:243-256

Kost GJ, Verity MA: A new variant of late-onset myophosphorylase deficiency. Muscle Nerve 1980 May-Jun; 3 (3):195-201

Oxenhandler R, Adelstein EH, Hart MN: Immunopathology of skeletal muscle—The value of direct immunofluorescence in the diagnosis of connective tissue disease. Hum Pathol 1977 May; 8:321-328

Pearson CM, Mostofi FK: The Striated Muscle. Baltimore, Williams & Wilkins, 1973

Amniocentesis

THE NEED TO study fetuses at risk for Rh incompatibilty led to the development of widespread interest in the physiopathology of amniotic fluid and the living cells it contains. Amniocentesis is a safe, well-established procedure done yearly on thousands of pregnant women at risk for a variety of disorders.

The amniotic fluid is generated by the fetal kidneys and lungs and constantly recycled through fetal swallowing. Most amniotic cells are dead or degenerating but a small proportion can be cultured. These cultures contain a variety of slow-growing epithelial cells and fast-growing mesenchymal cells that share many morphologic and biochemical properties with cultured skin fibroblasts.

Amniotic fluid contains phospholipids whose changing composition reflects fetal maturity. This has been exploited for the assessment and prevention of hyaline membrane disease. The association of elevated α-fetoprotein with neural tube defects has led to their early detection. Mucopolysaccaride analysis may occasionally help in the rapid identification of fetuses affected by a

mucopolysaccharide storage disorder. A variety of enzymes, including lysosomal hydrolases, can be analyzed but this has not led to practical diagnostic techniques. Most types of urine analysis can be carried out on the amniotic fluid, but this test is often neglected.

The study of freshly pelleted amniotic cells has limited applications but has allowed early diagnosis of selected storage disorders. Fabry's and Sandhoff's diseases and mucolipidosis IV can be detected by ultrastructural demonstration of characteristic inclusions that are not affected by cell degeneration.

Culture of amniotic cells is most commonly used for chromosome analysis and sex determination. Banding techniques have considerably increased the scope of identifiable chromosomal abnormalities. Sex determination has been used for families with crippling X-linked disorders not yet diagnosable in utero, such as Duchenne type muscular dystrophy or hemophilia. More than 30 types of lysosomal storage disorders can be diagnosed by enzyme determination on cultured amniotic cells. Using an elegant technique of DNA molecular hybridization, α-thalassemia can be diagnosed in amniotic cultures. This opens the way to the study of other mutations not expressed and therefore not directly detectable in these cells.

There is a crucial need for properly identifying fetuses at risk. This requires increasingly complex multidisciplinary cooperation. Too many genetic disorders are not recognized until two or more affected children are born in a family. Many probands hide behind such labels as cerebral palsy, multiple congenital abnormalities, autism or mental retardation. Only those families in which a specific chromosomal or biochemical abnormality has been found can benefit from prenatal diagnosis. Incomplete diagnosis, for example, "mucopolysaccharide storage disorder," not characterized by a comprehensive biochemical workup may prevent successful analysis of cultured amniotic cells in the time frame imposed by amniocentesis. Fluid may not be safely obtained before 12 to 14 weeks of pregnancy, and it takes at least three weeks but commonly six weeks to grow enough cells for a reliable analysis, whereas therapeutic abortion, if indicated, should be done no later than the 20th week. Ultramicrotechniques have been described that sometimes allow diagnosis on a single amniotic cell but large-scale practical application of this approach remains to be validated.

Screening groups with known risks, such as women 35 years old or older for trisomy 21, or Ashkenazi Jews for Tay-Sachs disease, has been highly successful. Most genetic disorders are undoubtedly rare but altogether they impose a disproportionate financial and psychological burden on families and, in the end, on the whole society.

Prenatal diagnosis has allowed a growing number of families at risk to have normal children by selected abortion of an affected fetus. Early treatment of abnormal fetuses would be much preferred but it is not conceivable in the near future.

The ethical issues involved have been hotly debated throughout the last decade. Genetic counseling is a relatively new discipline. No physician has a truly extensive experience in these problems, which vary widely with the specific disorders being monitored. A physician needs to guide and inform parents throughout the procedure. In most cases monitoring is of recessive disorders and therefore there is a 3:1 chance that the fetus will be normal or heterozygote. Some have advocated obtaining a primary commitment from parents that they will accept abortion if the fetus turns out to be affected. In practice some families who feel moral objections to a therapeutic abortion change their mind when confronted with the laboratory results. Meaningful counseling should not involve pressure or compulsion. Truly informed discussions whatever the ultimate parental decision are always mutually satisfying.

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REFERENCES

Galjaard H: Genetic Metabolic Diseases—Early Diagnosis and Prenatal Analysis. Amsterdam, Elsevier/North-Holland Biomedical Press, 1980

Motulsky AG, Lenz W: Birth defects. Amsterdam, Excerpta Medica, 1974

Wong V, Ma HK, Todd D, et al: Diagnosis of homozygous alpha-thalassemia in cultured amniotic-fluid fibroblasts. N Engl J Med 1978 Mar 23; 298(12):669-670

Aspiration of Thyroid Nodules by Fine Needles

INVESTIGATORS at the University of California at Los Angeles and other American hospitals have recently obtained good results in diagnosing thyroid nodules by aspiration. The only surprise is that we have taken so long to apply this simple technique to the problem of thyroid nodules, when aspiration of the thyroid gland has been a standard diagnostic procedure in Sweden and other European countries for almost 30 years. A good specimen of cells and fluid can be obtained from a thyroid nodule by one or two aspirations

through a fine (22 or 23) gauge needle. The thyroid aspiration through fine needles can be done in an office or clinic in several minutes without any special preparation, anesthesia or significant complication beyond a rare large hematoma. In many cases results of the procedure can be obtained in minutes or hours, and the cost is low compared with most diagnostic procedures.

Many factors affect the results. A primary factor is the nature of the underlying lesion. For example, an accurate and specific diagnosis can be obtained in most patients with papillary adenocarcinoma or chronic lymphocytic (Hashimoto's) thyroiditis. The findings in patients with colloid goiter are also characteristic and usually provide the correct diagnosis without thyroidectomy. Many cellular follicular nodules, especially well-differentiated follicular neoplasms, cannot be accurately subclassified, but patients with solitary follicular neoplasms can be segregated as candidates for an operation, sparing those with other nodules from needless or inappropriate operations. The experience of the person doing the aspiration and reading the slides affects the results of the procedure. Careful palpation is a requisite for a good aspiration, and an experienced person can actually feel the nodule with the needle during the aspiration and thus can correctly place the needle in the best spot for the aspiration. The specimen should be representative of the nodule.

There are tricks to making good smears from aspirate, and these can be learned. The pathologist interpreting the smears must be familiar with the general principles of cytology and know the specific microscopic features of a variety of nodular lesions of the thyroid gland. This knowledge can be obtained in part through independent study but should include training under experienced teachers and should be reinforced by active practice. The best results have been obtained when the same person does the aspiration and reads the smears. Good results can also be obtained when two people are involved if both are enthusiastic about the procedure and there is good communication between them. Clearly the results get better as the person or persons involved gain experience, and one should not be discouraged by the minor problems of establishing the procedure. Pathologists, endocrinologists, surgeons and physicians involved in the primary care of patients should give serious consideration to this simple, effective and inexpensive procedure for the diagnosis of thyroid nodules.

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REFERENCES

Chu EW, Hanson TA, Goldman JM, et al: Study of cells in fine needle aspirations of the thyroid gland. Acta Cytol 1979 Jul-Aug; 23:308-314

Lowhagen T, Granberg PO, Lundell G, et al: Aspiration biopsy cytology (ABC) in nodules of the thyroid gland suspected to be malignant. Surg Clin North Am 1979 Feb; 59:3-18

Silver CE, Loiodice J, Johnson JM, et al: Needle aspiration biopsy of thyroid nodules. Surg Gynec Obstet 1981; 152:469-472

Van Herle A, Rich P, Ljung BM, et al: The thyroid nodule. Ann Intern Med 1982 Feb; 96:221-232

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EDITORIALS

Correctable Errors in the Ordering of Diagnostic Tests

ELSEWHERE IN THIS ISSUE Albert Martin documents common errors in the ordering of diagnostic tests which in the aggregate can only add enormously to the costs of care. At first sight the remedy may seem simple enough: educate physicians in how to get the best value from the tests and procedures they order and apply the utilization review procedures which are now in more or less general use to this problem. There can be no quarrel with these approaches and they can and should be done.

But it should not be overlooked that motivations other than ignorance or even greed may encourage the ordering of diagnostic tests or procedures in greater numbers or more frequently than a purist might deem necessary. One of the more obvious is a perceived or real need for physicians and hospitals to practice defensive medicine, that is to have adequate documentation in the record in the event they are subsequently taken to court for alleged malpractice. Another, perhaps related to the above, can be a genuine diagnostic or therapeutic uncertainty on the part of a responsible physician who seeks any and all help possible from the laboratory.

Perhaps, in the long run, of equal or greater importance is the fact that physicians are paid poorly for cognitive or thinking services in comparison with payment for procedures. There is little financial incentive for a physician to take the time in a given case to think through the actual cost and benefit for each test or procedure when any and all can easily be ordered, to be on the safe side. And a corollary of this for both physicians and hospitals is that since payments by government and others for many services are below the actual cost to the physician and others of providing them, there is an incentive, be it conscious or unconscious, to balance the books with diagnostic tests and procedures, and at the same time to provide the patient with what is believed to be better care by ordering any test or procedure that might reasonably be indicated.

The points made by Martin are important. Clearly better care may be fewer tests and procedures. But more than education will be needed. Some shifts in financial incentives and payments in both office and hospital practice toward a more equitable recognition of the true value of various services will be required before this and many other problems in health care costs will ever really be solved.

—MSMW

ADDENDUM: *The American Society of Internal Medicine is seeking ways to gain greater recognition of physicians' cognitive services without adding to the overall costs of care. This is a much needed step and is to be encouraged and commended.*

—MSMW

Hyperalimentation in Cancer: Another Viewpoint

AS THE VOLUME of literature has collected on the use of intravenous hyperalimentation (IVH) in cancer patients, investigators have often taken sides in attempting to show its immense value or absolute lack of usefulness to the point of damning IVH as harmful. Such arguments have rekindled an interest in the cause of weight loss in cancer patients. Previous theories that the tumor acted as a *nitrogen trap,* thereby capturing amino acids and removing them from the host's amino acid pool, or of the tumor metabolizing glucose anaer-

obically, thereby releasing lactic acid that requires host energy to be recycled back to glucose, are being proposed as causes of cancer cachexia. I find it difficult, however, to reconcile the small volume of tumor relative to host mass seen in most cachectic cancer patients as primarily responsible for the syndrome of cancer cachexia via such postulated mechanisms. Persons with cancer do not adapt as well to the added insult of starvation as do those without cancer.[1] Normal homeostatic mechanisms exist to conserve lean tissue mass, but persons with cancer seem less able to make use of these lean tissue-conserving mechanisms and to decrease gluconeogenesis from protein stores in the presence of host starvation. Therefore, loss of lean tissue mass may continue unabated in a malnourished person with cancer if protein-calorie intake is inadequate.

Anorexia and weight loss associated with cancer often can be explained by the anatomic location of the malignant disease and by the anxiety associated with its symptoms. The effect of cancer on basal energy needs is variously reported as being unchanged, slightly increased or grossly decreased, depending on the tumor type studied or the time course of the natural history of the disease when energy expenditure is evaluated. Surgical intervention, radiation therapy and chemotherapy predictably increase the nutritional requirements and, at the same time, interfere with a patient's ability to eat. Most often, malnutrition in a patient with cancer results from the intensive efforts to eradicate the tumor by a combination of these forms of anticancer therapy. Each of these therapeutic steps is predicated on recovery from the preceding step. Unless adequate nutrient intake is ensured, a patient is at risk for protein-calorie malnutrition and may lose the benefit of the combined effects of surgical procedures, chemotherapy and radiation therapy. Absorption of nutrients via a functional gastrointestinal tract is the best means of maintaining adequate nutrition; however, nutritional supplementation via the gastrointestinal tract can be time-consuming or the gastrointestinal tract may be unavailable for nutrient administration. Under these circumstances, IVH may be of value.

Elsewhere in this issue, Karlberg and Fischer have reviewed and given an opinion on the state of the art of IVH in cancer. My point of view differs from theirs in a number of ways, as will be described in this editorial. The authors have intertwined data from rats and human beings in one instance to argue against nutritional support and for starvation during chemotherapy treatment. Yet they point out that a negative energy state makes a cancer patient "more vulnerable to acute stress factors such as infections and surgical trauma." In other words, morbidity and possibly mortality may be increased during chemotherapy and after surgical procedures in malnourished patients with cancer. Proponents of IVH, such as myself, have used it for nutritional repletion specifically to limit such complications. I agree that "hyperalimentation as such is of minor importance as an antitumor treatment regimen." I am totally unaware that anyone has ever ascribed any anticancer properties to IVH. Its use is to nutritionally replenish a malnourished patient.

The authors have analyzed what seems to me to be a relatively simple problem of malnutrition with a straightforward therapeutic solution in a way as to make the problem more complicated. In two instances, the authors are quite accurate: (1) there is no evidence that IVH accelerates tumor growth in human beings and (2) quality of life may be improved by improving a patient's ability to tolerate the side effects of antineoplastic therapy. Interestingly, in most of the referenced articles, malnourished patients better tolerated oncologic therapy because IVH was used to gain some degree of nutritional repletion before beginning cancer treatment. Yet, in the authors' opinion there is no justification for nutritional repletion between oncologic treatment regimens to correct antecedent malnutrition, no justification for using IVH preoperatively in malnourished patients until anabolism is attained and no justification for the use of IVH in a patient with cancer who has become malnourished because of prior oncologic therapy and who cannot regain weight and strength by enteral alimentation. I disagree. There may be strong justification for the use of IVH in each of these circumstances. To recommend IVH only concurrent with oncologic therapy does not allow for any degree of nutritional restoration of a malnourished patient before further catabolic stress. Such a therapeutic approach may negate the use of the nutritional solutions.

The formula for IVH as quoted by Karlberg and Fischer is insufficient in protein. They recommend a daily infusion of between 1,700 and 3,400 calories as glucose, with only 42.5 grams of protein. Such a formulation would result in weight gain primarily as fat and water and may explain why they have noted little gain in lean body mass in their

patient population. I hope immediate nutritional support of starved or traumatized patients has not become a *routine* part of treatment. Nutritional therapy should be individually tailored to meet specific treatment objectives and there should be very little routine about it.

The authors state that "there is not a single properly conducted randomized prospective trial that shows a statistically significant beneficial effect in tumor patients treated with nutritional support." My question is, has there been a single, properly controlled, randomized prospective trial? Malnutrition is a poor prognostic indicator for response to chemotherapy. Whether or not nutritional repletion, either by enteral or parenteral methods, can reverse malnutrition and convert a predictably poor responder to chemotherapy into a good responder remains unknown. In many of the studies cited in this review, patients with only minimal degrees of malnutrition were entered into the randomization process, or if malnourished patients were in the studies, little data on the nutritional efficacy of IVH are given to allow an evaluation of the capacity of the nutrient solutions to lead to nutritional repletion. In a study by Nixon and co-workers,[2] patients with colon cancer treated with 5-fluorouracil (5-FU) and randomly assigned to receive IVH had a significantly shorter survival time than similarly treated patients not nutritionally supported with IVH. A critical appraisal of this report shows that (1) the number of patients in this study was small, (2) distribution of metastatic sites was 1.95 per patient for the IVH group and only 1.2 per patient for the control group, (3) the median duration of disease was 11.5 months for the IVH group and 15 months for the control group, (4) the response to 5-FU was poor in both groups, 15 percent versus 12 percent, respectively, and (5) there was no mention of weight gain or change in nutritional measurements. The IVH group had more metastatic sites and a shorter duration of disease, indicating a more rapidly progressing metastatic process. The study of Nixon and his collaborators, therefore, indicates that IVH has no effect on rapidly progressive malignant disease, particularly if response to oncologic therapy is poor. This study does not indicate that IVH is necessarily dangerous to this patient population, as has been concluded by others.

It is important to know whether a previously malnourished patient who has been nutritionally replenished with IVH is a better candidate for response to antineoplastic therapy than is a malnourished counterpart. The answer to such a question may not be known until a study combining at least the following necessary elements is done:

- a good definition of malnutrition,
- random assignment of malnourished patients between conventional nutritional maintenance and IVH,
- a control group of well-nourished patients on conventional nutritional maintenance,
- cancer that is moderately responsive to drugs,
- drugs with moderate gastrointestinal toxicity and
- tumor response to chemotherapy correlated with nutritional response to nutritional therapy.

Such studies are quite necessary because overinterpretation of the available data or bias for or against the use of IVH in patients with cancer could result in its being withheld when needed or used when unwarranted.

For IVH to be effective, it must be given for a long enough time for an anabolic response to be seen and for such a response to progress until secretory proteins, lean body mass and immune response have returned toward normal levels. Just because IVH is used does not necessarily mean a patient will become nutritionally replenished. The induction of anabolism depends on the content, method and time of administration of the IVH solutions, the initial and continuing catabolic response of a patient, the degree of initial malnutrition, the energy expenditure of a patient required during oncologic therapy and, last but not least, the expertise of the physician using IVH. Those clinical studies that fail to include sequential nutritional assessment to identify the effect of IVH on net protein synthesis cannot justifiably state that "nutritional repletion" of the host had no effect on the response of a particular tumor to a chemotherapeutic regimen or on the response of a host to surgical trauma. Such are the randomized, prospective studies of Holter and Fischer[3] and Preslow and associates[4] in which patients received IVH for perioperative periods too short to result in nutritional restoration. In studies with such a design, an effect on mortality and morbidity from "preoperative nutritional repletion" would not be anticipated. These studies,

however, have been used to negate the effect of the use of preoperative IVH in malnourished cancer patients. Muller and Mullen and their collaborators[5,6] now have impressive data to indicate that preoperative nutritional repletion of malnourished cancer patients reduces morbidity and mortality from surgical procedures.

My review of the available data indicates that IVH should be reserved for truly malnourished cancer patients for whom antineoplastic therapy is available. Well-nourished patients and malnourished patients for whom there is no available oncologic therapy have benefited little or not at all from the use of IVH. Nutritionally intact patients gain weight primarily as water and fat and would be subjected unnecessarily to the inherent complications of IVH. Terminally ill patients may feel somewhat better during IVH infusion, but this effect rapidly ceases once IVH is discontinued. Prolongation of pain for a patient and anguish for the family certainly are not justifiable indicators for the use of IVH in patients with cancer. For those patients in whom oncologic therapy is a reality, cancer cachexia should no longer be a contraindication to treatment. Adequate nutritional repletion should be undertaken before the indicated antineoplastic therapy. Attention to proper metabolic, physiologic and nutritive restoration and maintenance should minimize the complications from all modalities of oncologic therapy. For malnourished patients who require nutritional rehabilitation to become candidates for appropriate oncologic therapy, IVH can be a quite useful part of the armamentarium of a practicing oncologist.

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REFERENCES

1. Brennan MF: Uncomplicated starvation versus cancer cachexia. Cancer Res 1977 Jul; 37:2359-2364

2. Nixon DW, Moffitt S, Lawson DH, et al: Total parenteral nutrition as an adjunct to chemotherapy of metastatic colorectal cancer. Cancer Treat Rep (In press), 1982

3. Holter AR, Fischer JE: The effects of perioperative hyperalimentation on complications in patients with carcinoma and weight loss. J Surg Res 1977 Jul; 23:31-34

4. Preshaw RM, Attisha RP, Hollingsworth WJ, et al: Randomized sequential trial of parenteral nutrition in healing of colonic anastomoses in man. Can J Surg 1979; 22:437-439

5. Muller JM, Dienst T, Arndt M, et al: Der Einfluss der präoperativen hochkalorischen parenteralen Ernährung auf die postoperative Komplicationsrate in der Tumorchiurgie, *In* Muller JM, Pichlmaier H (Eds): Hochkalorischen Parenterale Ernährung. Berlin, Springer-Verlag, 1981, pp 161-173

6. Mullen JL, Buzby GP, Matthews DC, et al: Reduction of operative morbidity and mortality by combined preoperative and postoperative nutritional support. Ann Surg 1980; 192:604-610

New Insights Into Coronary Vasospasm

IN 1959 Prinzmetal and co-workers[1] described a variant form of angina pectoris in a collected series of 32 patients and, with remarkable clarity of perception, proposed pathophysiologic mechanisms that have proved largely correct. Variant angina, they hypothesized, occurred when an epicardial coronary artery, narrowed by atherosclerosis, became temporarily occluded due to a "normal increase in tonus of the vessel wall."[1]

Also in 1959 Sones and colleagues[2] described selective coronary arteriography. This technique, particularly in combination with ergonovine provocation,[3] has become the gold standard for documentation of vasospastic coronary occlusion. But despite a fairly complete angiographic and clinical characterization of variant angina, the underlying mechanisms of transient arterial occlusion remain obscure. The Specialty Conference presented by Drs. Ginsburg, Schroeder and Harrison in this issue summarizes the clinical approach to coronary vasospastic disorders used at the Stanford University Medical Center and also discusses the vascular smooth muscle cell in relation to spasm mechanisms and to its therapy. In collaboration with Ross and associates[4] at the University of California, Los Angeles, and in subsequent studies in their own laboratories, this group is adding an important new dimension to our understanding of spasm in their studies of coronary arterial segments obtained from the freshly excised hearts of human transplant recipients. Because human coronary smooth muscle appears to have unique contractile properties,[4] this approach is generating useful new insights into cellular mechanisms of coronary spasm.

A comprehensive understanding of variant angina must accommodate many clinical and pathologic observations. Angiographically, coronary atherosclerosis of typical severity is present in most patients,[5] though 5 percent to 10 percent of spastic segments are classified as "normal" on the angiogram. It is a common misconception that spasm usually occurs in normal coronary arteries; in fact, this occurs infrequently,[6] if at all. Spasm is usually localized in one diseased arterial segment and occurs repeatedly at the same site. Clinically, episodes of variant angina occur at rest or

during ordinary activity, without an antecedent increase in myocardial oxygen requirement; pain sometimes comes in waves at ten-minute intervals. Pain may have a diurnal variation, occurring most frequently about 6 AM. The anginal syndrome may become quiescent for several months to years; however, myocardial infarction occurs in 15 percent to 20 percent of acute cases[7,8] and death in about 5 percent.[7,8] Acute emotional outbursts appear not to precipitate variant angina attacks, but pain may be provoked by a variety of physical stresses, including treadmill exercise, hyperventilation, cold pressor and isometric handgrip. Pharmacologic induction of spasm and pain has been reported with a long list of agents including α-adrenergic agonists (norepinephrine, epinephrine plus propranolol), β-antagonists (propranolol), parasympathomimetic agents (methacholine), direct contractile stimulants (ergonovine maleate), alkalinizing agents (TRIS buffer [tromethamine]) and histamines.

Is *hypercontractility* of coronary smooth muscle necessary to account for vasospastic occlusion or is it simply that certain morphologic and hemodynamic features of coronary atherosclerosis amplify the effects of ordinary coronary vasomotor activity to induce symptoms? And what are *ordinary* amounts of smooth muscle contraction? To answer these questions, we have used a computer-assisted angiographic method[9] to measure the magnitude of induced vasomotor changes in lumen caliber in normal and diseased coronary segments.[10-12] Normal portions of epicardial coronary arteries constrict by about 9 percent in lumen diameter following α-adrenergic stimulation[10,11] and by 18 percent following ergonovine.[10] Normal segments in patients with variant angina respond exactly like those in patients with exertional angina.[11] However, in patients who have a clinical presentation with vasospastic angina, a diseased arterial segment, which is *hyperreactive* to vasoconstrictor stimuli, will almost always be found in the appropriate artery. Thus it is not the patient, or the entire coronary tree, or the implicated artery that is abnormally responsive to vasoconstrictor stimulation; it is one particular arterial segment (usually diseased, but not necessarily the most severe stenosis in a given patient) that is abnormally vasoactive. Segmental coronary hyperreactivity has several possible mechanisms:

- Sympathetic innervation or activity may be locally increased. As discussed in the Specialty Conference, this appears to be an unlikely triggering mechanism for focal spasm.
- Vasoconstrictor receptor density or sensitivity may be segmentally increased. Indeed, there is in vitro evidence suggesting that this occurs in cholesterol-induced atherosclerosis.[13]
- Local flow factors or shear-induced endothelial damage may increase the *availability* of circulating vasoactive substances to the medial smooth muscle cells.
- An atherosclerotic plaque may arise from one side of the vessel resulting in a narrowed lumen that is eccentrically located and partially circumscribed by an arc of relatively normal arterial wall. This common lesion morphology greatly magnifies the obstructing effect of ordinary amounts of smooth muscle contraction.[11]
- Mural thrombus, localized to atherosclerotic segments, can release several known vasoconstrictor substances. This does not appear to be a trigger mechanism for spasm.[14]
- Powerful spontaneous calcium-dependent phasic contractions have been shown in human coronary arteries by Ross[4] in collaboration with the Stanford investigators. These contractions occurred with a periodicity of seven to ten minutes, were intensified by ergonovine, norepinephrine and potassium, and were diminished by low calcium, by verapamil and by nitroglycerin. This contractile activity may be segmentally localized due to atherosclerosis. It may be triggered by an as-yet-unknown endogenous substance or, as Ross has suggested, by the absence of an inhibitor substance.
- Tight-junction electrical communications between arterial smooth muscle cells are necessary if focal cellular depolarization is to spread and result in a concerted segmental contracture. While these nexus have been shown ultrastructurally, we know little about the factors that modulate their function.
- Intraluminal pressure falls in a constricting segment due to viscous and kinetic losses. A vicious cycle of falling pressure and further luminal collapse can occur. This phenomenon has been demonstrated experimentally[15,16] and observed in patients.[17]

The relative importance of each of the above mechanisms remains to be determined, but

present evidence leads most directly to the following interpretations. Partial atherosclerotic luminal narrowing—by focal atheroma or by diffuse intimal thickening—is a common denominator among the coronary vasospastic syndromes. Histologic features of the cross-sectional lesion morphology form the underlying anatomic substrate for vasospastic obstruction.[11] A second common denominator is the segmental activation, by any of a number of proposed triggering mechanisms, of the calcium-dependent final pathway of smooth muscle contraction.[18] Of these triggering mechanisms, α-adrenergic stimulation is relatively weak and, though it may modulate the exertional angina threshold, it appears not to trigger most episodes of variant angina. The recent discovery of a more powerful spontaneous contractile activity in human coronaries[4] may lead us to the principal triggering mechanism. Finally, recent observations[15-17] suggest that hemodynamic factors play a more important role in coronary luminal collapse than previously considered.

Thus in the spectrum of coronary vasospastic disorders that includes variant angina at one extreme, there is a dynamic interplay among mechanisms of cellular activation and contraction, atherosclerosis and hemodynamic factors. Variant angina will eventually be understood in terms of these interactions, and not simply in terms of "abnormalities at the single cell level." Our understanding of the key role of calcium in cellular contraction and the observed beneficial effect of the calcium slow-channel blocking drugs opens an important avenue for therapy. But the triggering events and principal dynamic interactions in coronary spasm remain obscure. Their eventual understanding will lead to more specific forms of therapy. We look to the studies of the Stanford group for further insights into these triggering mechanisms.

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REFERENCES

1. Prinzmetal M, Kennamer R, Merliss R, et al: A variant form of angina pectoris: Preliminary report. Am J Med 1959; 27:375-388

2. Sones FM Jr, Shirey EK, Proudfit WI, et al: Cine coronary arteriography. Circulation 1959; 20:773-774

3. Heupler FA, Proudfit WL, Razavi M, et al: Ergonovine maleate provocative test for coronary arterial spasm. Am J Cardiol 1978; 41:631-640

4. Ross G, Stinson EB, Schroeder J, et al: Spontaneous phasic activity of isolated human coronary arteries. Cardiovasc Res 1980; 14:613-618

5. Maseri A, Severi S, DeNes M, et al: Variant angina: One aspect of a continuous spectrum of vasospastic myocardial ischemia—Pathogenetic mechanisms, estimated incidence and clinical and coronary arteriographic findings in 138 patients. Am J Cardiol 1978 Dec; 42:1019-1035

6. MacAlpin RN: Relation of coronary arterial spasm to sites of organic stenosis. Am J Cardiol 1980; 46:143-153

7. Severi S, Davies G, Maseri A, et al: Long-term prognosis of variant angina with medical treatment. Am J Cardiol 1980; 46: 226-232

8. MacAlpin RN, Kattus AB, Alvaro AB: Angina pectoris at rest with preservation of exercise capacity—Prinzmetal's variant angina. Circulation 1973; 47:946-958

9. Brown BG, Bolson EL, Frimer M, et al: Quantitative coronary arteriography: Estimation of dimensions, hemodynamic resistance and atheroma mass of coronary artery lesions using the arteriogram and digital computation. Circulation 1977; 55:329-337

10. Brown BG, Bolson E, Dodge HT, et al: Verapamil, a mild epicardial coronary dilator, inhibits sympathetic and ergonovine-induced coronary constriction in humans. Circulation 1981; 64: (suppl IV) IV-150

11. Brown BG: Coronary vasospasm: Observations linking the clinical spectrum of ischemic heart disease to the dynamic pathology of coronary atherosclerosis. Arch Intern Med 1981; 141: 716-722

12. Brown BG, Bolson EL, Petersen RB, et al: Mechanisms of nitroglycerin action: Stenosis vasodilation as a major component of the drug response. Circulation 1981; 64:1089-1097

13. Henry PD, Yokoyama M: Supersensitivity of atherosclerotic rabbit aorta to ergonovine—Mediation by a serotonergic mechanism. J Clin Invest 1980 Aug; 66:306-313

14. Robertson RM, Robertson D, Roberts LJ, et al: Thromboxane in vasotonic angina pectoris with evidence from direct measurements and inhibitor trials. N Engl J Med 1980; 304:998-1003

15. Santamore WP, Walinsky P: Altered coronary flow responses to vasoactive drugs in the presence of coronary arterial stenosis in the dog. Am J Cardiol 1980; 45:276-285

16. Schwartz JS, Carlyle PF, Cohn JN: Effect of coronary arterial pressure on coronary stenosis resistance. Circulation 1980; 61:70-76

17. Brown BG, Josephson MA, Petersen RB, et al: Intravenous dipyridamole combined with isometric handgrip for near-maximal acute increase in coronary flow in patients with coronary disease. Am J Cardiol 1981; 48:1077-1085

18. Adelstein RS, Hathaway DR: Role of calcium and cyclic adenosine 3':5' monophosphate in regulating smooth muscle contraction. Am J Cardiol 1979; 44:783-787

CASE REPORTS

Refer to: Giles DJ, Nixon GW, Middleton AW Jr: Vaginal ectopic ureter: A continuing diagnostic challenge. West J Med 1982 May; 136:436-439

Vaginal Ectopic Ureter: A Continuing Diagnostic Challenge

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ECTOPIC URETER DRAINING to the vagina is a rare congenital malformation that causes significant symptoms and morbidity and is rarely considered early. The symptomatology is pathognomonic but variable. In the cases reported here, vaginal discharge and chronic perineal wetness were the major symptoms, rather than the more classic urinary incontinence. In any case where this entity is clinically suspected, aggressive workup should begin with intravenous urography, followed by ultrasonography and vaginography. Depending on results of ultrasonogram or vaginogram further workup should be pursued.

Reports of Cases

CASE 1. A 4-year-old girl presented with a history of urinary frequency, "no bladder control" and recurrent yellowish vaginal discharge since toilet training, which had occurred at age 3. Voiding cystourethrography (VCU) elicited no abnormality. Intravenous urography (IVU) showed a normal right kidney but nonvisualization on the left. At cystoscopy a left ureteral orifice could not be identified. Over the next two years the patient had multiple febrile illnesses that were often associated with left abdominal pain. Voiding cystourethrography, intravenous urography and cystoscopy were repeated with no change in the findings. At 6 years of age, intravenous urography with tomography failed to demonstrate a left kidney.

Because of suspicion of an ectopic ureter draining a small left kidney, an aortogram was done, which failed to show a left renal artery. Through the ensuing four years the patient continued to have perineal wetness, recurrent vaginal discharge and recurrent episodes of fever and left flank and left abdominal pain. At 10 years of age a vaginogram (Figure 1) showed retrograde filling of a left ureter and renal collecting structures.

The patient subsequently underwent a left nephroureterectomy. At operation the left kidney was very small (3 by 2 by 1 cm) and there was duplication of the collecting structures. The lower pole portion of the kidney was very hypoplastic and its ureter was atretic in its proximal portion. The upper pole collecting system drained ectopically to the apex of the vagina. Histologic examination revealed renal dysplasia and chronic inflammatory change. During the ensuing six years the patient has done well with no further perineal wetness or vaginal discharge.

CASE 2. A 7-year-old girl presented with a four-year history of vaginal discharge and persisting perineal wetness. These complaints had been evaluated by at least five different physicians, one of whom had treated her for gonorrhea. The patient had had episodes of left lower abdominal pain but none were associated with fever. Intravenous urography (Figure 2) revealed a so-called cystic area in the upper pole of the left kidney; the collecting structures of the lower pole area appeared normal but displaced by the upper pole cystic mass. An ectopically draining ureter was suspected, so a vaginogram was done but failed to show the suspected findings. Ultrasonography demonstrated a sonolucent area in the left upper pole. A 20-gauge sheathed needle was inserted percutaneously in this cystic area and antegrade pyelography was done (Figure 3), demonstrating a duplicated collecting system with the upper pole portion draining ectopically into the vagina. Methylene blue instilled into this system appeared in the vagina in 30 minutes. Subsequent cystoscopy was normal and vaginography under anesthesia did not show the ectopic ureteral orifice. A left

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Figure 1.—Vaginogram from Case 1: The dilated distal left ureter and dilated duplicated collecting system are opacified with contrast material.

Figure 2.—Intravenous urogram film from Case 2: Dilated duplicated collecting system compresses and distorts the lower pole collecting system and gives the appearance of an upper pole intrarenal mass lesion.

upper heminephrectomy and ureterectomy were done and the patient has since been asymptomatic.

Discussion

Ectopic ureter results from faulty embryogenesis.[1-3] Ectopic drainage can be to any structure derived from the wolffian duct or at sites of ectopic wolffian duct tissue.[4] Ectopic drainage sites in a female patient are the urethra, vagina, cervix, uterus, fallopian tube or rectum.[5] Approximately 80 percent of all ectopic ureters are associated with duplicated collecting systems and the more cephalad system is nearly always the one that drains ectopically.[4,6,7] There is usually high-grade obstruction of the ectopically draining ureter. The vagina is an infrequent site for ectopic drainage (8 percent to 27 percent in several series); the lower portion of the bladder and urethra are more frequently involved.[5,6,8-10] As a general rule, the farther the ectopic ureteral orifice is from its normal location on the bladder floor, the more dilated will be the ureter and the more dysplastic will be its kidney.[11]

The history obtained from a patient with vaginal ectopic ureter is usually characteristic. Urinary incontinence or chronic perineal wetness

Figure 3.—Antegrade pyelogram from Case 2: The dilated duplicated collecting system is seen almost in its entirety. Contrast material in the bladder from previous intravenous urogram obscures the site of entry of the ectopic ureter into the vagina.

after toilet training is highly suggestive of this entity.[3,5,12-14] Such incontinence occurs despite maintaining a normal voiding pattern and may be present only when the patient is upright. This occurs because the involved portion of the kidney functions poorly and the involved ureter is usually dilated and acts as a reservoir in recumbency.[4,9] Other symptoms include vaginal discharge, abdominal pain, back pain and recurrent febrile illnesses.[12-16] Despite the characteristic symptomatology, patients often must consult multiple physicians and have extensive, exhaustive and often duplicated workups.[5,17] Nearly two thirds of patients reach adulthood before their condition is diagnosed and this often results in considerable physical and psychological morbidity.[6,13] Probably most patients with vaginal ureteral ectopia have no positive physical findings, though some will have a palpable abdominal mass or palpable ridge in the vaginal wall caused by the dilated obstructed distal ureter.[9]

Histologically the affected kidney frequently shows severe dysplastic changes. The renal pathology is not necessarily a reflection of primary renal dysplasia (multicystic dysplastic kidney) but can be due to long-standing obstruction or infection or both.[2,11,18]

It is mandatory that an exhaustive evaluation be done to exclude ureteral ectopia whenever a suggestive history exists. Multiple radiologic procedures are available that give an accurate evaluation of this condition. Intravenous urography should be the initial procedure.[17] Duplication with diminished function or nonfunction in the upper pole or unilateral nonfunction or diminished function in the proper clinical setting is very suggestive of this diagnosis and would justify further evaluation. Ultrasonography is useful when a duplicated system with poor function of the ectopically draining system is suspected. This may show the dilated upper pole collecting system and ureter that may not be seen on intravenous urography because of poor function. Also, with unilateral absent or diminished function on intravenous urography, ultrasound evaluation may demonstrate a small kidney and dilated collecting structures. Vaginography[19,20] is a definitive method of evaluation if there is retrograde filling of the ectopic ureter but failure to demonstrate this does not exclude the presence of an ectopic ureter.

These three studies should constitute a minimal evaluation if vaginal ectopic ureter is suggested by clinical history. If ultrasound examination shows a so-called cystic area or hydronephrosis, antegrade injection of contrast medium following percutaneous insertion of a catheter into the renal collecting system can be done. This will usually show the site of ureteral drainage but, if indeterminate, methylene blue or another dye can be instilled and the site of drainage subsequently identified. Cystoscopic and vaginoscopic evaluation are mandatory in attempting to identify the site of ectopic drainage. The ipsilateral absence of a ureteral orifice suggests the presence of an ectopic ureter (see Figure 4).

The surgical management of the ectopic ureter

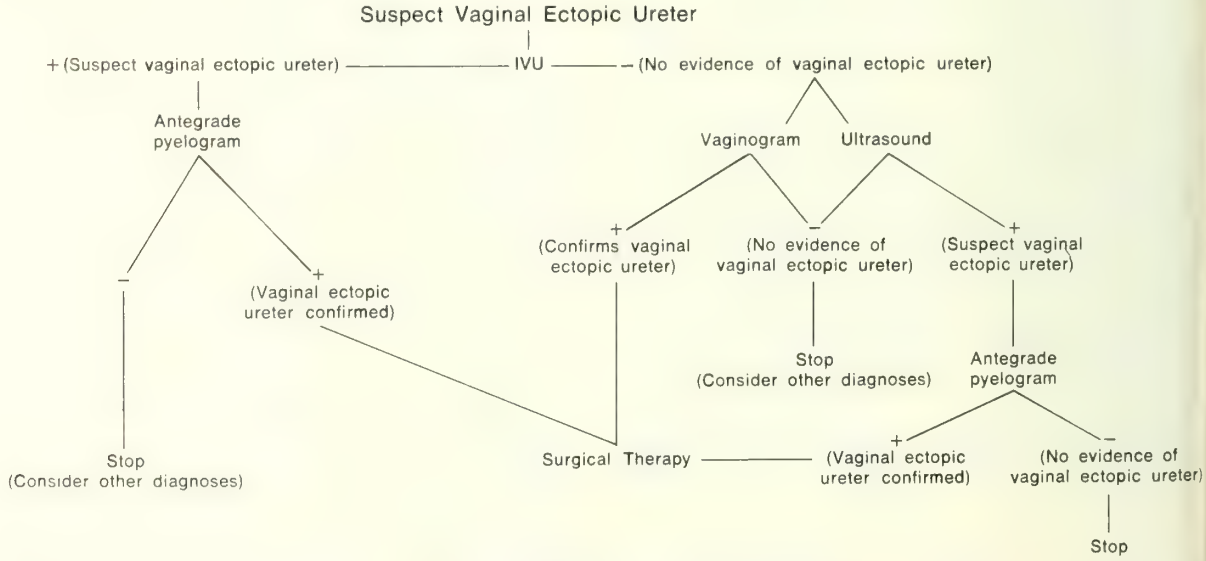

Figure 4.—Schematic of diagnostic workup and treatment for suspected vaginal ectopic ureter. + = findings that confirm the diagnosis, – = test fails to confirm diagnosis.

depends on the degree of function in the renal segment drained by the ureter. Most ectopic ureters opening into the vagina drain from renal segments so hydronephrotic and dysplastic that a nephroureterectomy is the best treatment.[3] Most such ureters drain the upper pole of a duplicated system, though occasionally a single ectopic ureter is found draining a dysplastic kidney.[21]

Occasionally an ectopic ureter is encountered with sufficient function remaining to warrant an attempt at salvage. This decision might be made when function in the renal segment is demonstrated on intravenous urography or on renal scan, or by the finding at operation of enough renal parenchyma to suggest future renal functional return. Salvage can be accomplished by a variety of methods involving reimplantation of the ectopic ureter.[5,22]

Some authors suggest removing the upper pole of the kidney and proximal portion of its ureter and leaving the distal ectopic ureter intact because of their fear of devascularizing or otherwise injuring the distal portion of the companion ureter.[3] We have not chosen this approach as it appears to us that when the child becomes a sexually active adult, the retained segment of dilated, poorly draining ureter must certainly serve as a constantly infected perivaginal diverticulum. Other problems may arise from the retained ureteral segment as well.[23] Instead, we remove the ureter to its junction with the vagina and oversew the vagina at that point. Meticulous attention to surgical technique will prevent injury to the adjacent distal ureter.

Conclusion

Vaginal ectopic ureter results from faulty embryogenesis and results in characteristic symptomatology. Extensive evaluation to exclude the diagnosis is mandatory because failure to diagnose the condition can lead to significant psychologic and physical morbidity. Workup involves a logical sequence of radiographic and endoscopic studies and can be done safely and rapidly. Effective curative surgical therapy is available.

REFERENCES

1. Delph WI, Patrick CE, Schlossberg I: Ureteral duplication with obstruction. J Natl Med Assoc 1976 Mar; 68(2):125-128
2. Mackie GG, Awang H, Stephens FD: The ureteric orifice: The embryologic key to radiologic status of duplex kidneys. J Pediatr Surg 1975 Aug; 10(4):473-481
3. Malek RS, Kelalis PP, Stickler GB, et al: Observations on ureteral ectopy in children. J Urol 1972 Feb; 107(2):308-313
4. Hartman GW, Hodson C: The duplex kidney and related abnormalities. Clin Radiol 1969 Oct; 20:387-400
5. Leary FJ, Bass RB Jr, Symmonds RE: Watery vaginal discharge in a young woman (Clinical Conference). J Urol 1979 Aug; 122(2):226-229
6. Burford C, Glenn J, Burford E: Ureteral ectopia: A review of the literature and two case reports. J Urol 1949 Aug; 62(2): 211-218
7. Schulman CC: The single ectopic ureter. Eur Urol 1976; 2(2):64-69
8. Blundon K, Lane J: Diagnostic difficulties in ureteral ectopia. J Urol 1960 Sep; 84(3):463-469
9. Allerker A: The extravesical ectopic ureter. Br J Surg 1958 Jan; 45(192):344-353
10. Greene LF: Ureteral ectopy in females. Clin Obstet Gynecol 1967 Mar; 10(1):147-154
11. Johnston JH: Problems in the diagnosis and management of ectopic ureters and ureteroceles, *In* Problems in Pediatric Urology. Amsterdam, Excerpta Medica, 1972, pp 57-78
12. Brannan W, Henry HH II: Ureteral ectopia: Report of 39 cases. J Urol 1973 Feb; 109(2):192-195
13. Greene LF: Ureteral ectopy in females. Surg Clin North Am 1959 Aug; 39(4):989-994
14. Ogawa A, Kakizawa Y, Akaza A: Ectopic ureter passing through the external urethral sphincter: Report of a case. J Urol 1976 Jul; 116(1):109-110
15. Persky L, Noseworthy J: Adult ureteral ectopia. J Urol 1976 Aug; 116(2):156-159
16. Simms MH, Higgins PM: Diagnosis of the occult ectopic ureter in a duplex kidney. J Urol 1975 Nov; 114(5):697-699
17. Borski A, Parsons R: Ureteral ectopia. US Armed Forces Med J 1960 Aug; 9(3):1213-1216
18. Gibbons MD, Duckett JW Jr: Single vaginal ectopic ureter: A case report. J Urol 1978 Oct; 120:493-495
19. DeShadarevian JJ, Ward JN, Lavengood RW: Simple method for diagnosis of ureterovaginal fistula. Urology 1979 Sep; 14(3):265-266
20. Katzen P, Trachtman B: Diagnosis of vaginal ectopic ureter by vaginogram. J Urol 1954 Nov; 72(5):808-811
21. Mandell J, Stevens PS, Lucey DT: Management of the unsuspected ectopic ureterocele. J Urol 1978 Oct; 120(4):496-498
22. Moore T: Ectopic openings of the ureter. Br J Urol 1952 Mar; 24(1):3-18
23. Kelalis PP, Kind LR, Belman AB: Clinical Pediatric Urology. Philadelphia, WB Saunders, 1976, pp 528-541

Refer to: Goldbach PD, Mohsenifar Z, Abraham JL, et al: Talcum powder pneumoconiosis: Diagnosis by transbronchial biopsy using energy-dispersive x-ray analysis. West J Med 1982 May; 136:439-442

Talcum Powder Pneumoconiosis

Diagnosis by Transbronchial Biopsy Using Energy-Dispersive X-ray Analysis

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ALTHOUGH COSMETIC TALC is widely used as a dusting powder, it is not generally considered to be a hazard.[1] During its usual use, relatively small quantities are inhaled,[2] and inhaled particles are efficiently cleared by the tracheobronchial tree.

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Whereas cosmetic talcum products sold in the United States contain variable amounts of pure talc, they are considerably less contaminated with asbestos and other minerals than are commercial grades of talcum.[3] In people who are exposed to commercial grades of talc, a clinical syndrome may develop with pulmonary fibrosis resembling that produced by exposure to asbestos. The effects may be due to contamination by asbestos, but the fibrous form of talc itself may play a role as it has been shown that platelike crystals can be taken up by tissue phagocytes and are potentially fibrogenic.[4] There have been few reports of lung disease in adults attributed to the inhalation of cosmetic talc.[5-7] We report a case of pulmonary talcosis due to the intentional sniffing of large quantities of cosmetic talcum powder.

Report of a Case

A 40-year-old woman was seen for preoperative pulmonary evaluation during a bout of cholecystitis. She noted a 15-year history of gradually progressive exertional dyspnea and was now dyspneic after walking 1½ blocks. There was no history of cough, wheeze or fever or of tuberculosis or pneumonia. She had a 40-pack-year smoking history and was currently smoking 1½ packs a day. The patient was a housewife, had worked outside the home as a receptionist for only six months ten years ago and gave no history of exposure to asbestos, other silicates or dusty environments. She said she had no history of drug abuse.

The physical examination was remarkable for tachypnea with a respiratory rate of 20 per minute, scattered rhonchi and decreased breath sounds at both bases. Chest roentgenogram showed a diffuse reticulonodular interstitial infiltrate with conglomerate masses in both midlung zones. There was evidence of retraction of these masses toward the hila and volume loss was seen at both bases. There was no notable change in comparison with films obtained eight months before this admission. No pleural plaques were noted (Figure 1). Pulmonary function testing showed combined moderate obstructive and restrictive defects. Single-breath diffusing capacity for carbon monoxide was 58 percent of its predicted value and was normal after correcting for the lung volume at which it was measured. Sec-

Figure 1.—Photograph of a chest roentgenogram showing a diffuse reticulonodular infiltrate with conglomerate masses in both midlung zones.

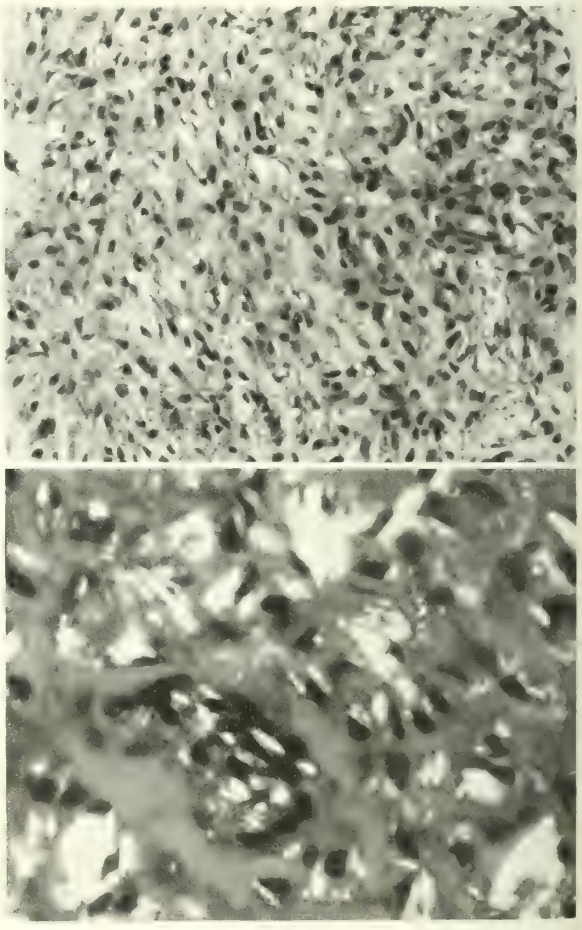

Figure 2.—Photograph of a transbronchial biopsy specimen showing dense cellular tissue containing many strongly birefringement particles. (**Top,** reduced from magnification ×300.) **Bottom,** higher magnification (reduced from ×1,000) partially polarized.

ond-strength purified protein derivative (PPD) and coccidioidin skin tests were negative and gallium scan of the lung showed diffuse uptake in the midlung areas. Fiberoptic bronchoscopy did not reveal endobronchial lesions and transbronchial biopsy histologically yielded densely cellular tissue infiltrated with macrophages and giant cells. There was no necrosis and special stains were negative for acid-fast bacilli and fungi. Under polarized light there were innumerable birefringent platelike particles seen throughout the tissue specimen (Figure 2).

A single section from the hematoxylin- and eosin-stained slide was examined using scanning electron microscopy (SEM) with energy-dispersive x-ray analysis (EDXA).[8] SEM revealed innumerable intracellular platelike talc particles and many fibers (Figure 3). On EDXA over 95 percent of the particles were found to be composed of magnesium (Mg) and silicon (Si) in a ratio consistent with talc ($Mg_6Si_8O_{20}[OH]_4$) (Figure 4). Smears of sputum were similarly examined by both light microscopy and SEM and innumerable talc-laden intact macrophages plus ferruginous bodies were identified (Figure 5).

After the diagnosis was established, detailed questioning revealed that the patient had repeatedly sniffed handfuls of talcum powder two or three times daily for one to two months during two bouts of postpartum depression and years ago. She said there had been no recent episodes of sniffing talcum. Follow-up pulmonary function tests obtained a year after the initial evaluation were essentially unchanged.

Figure 3.—Photograph of lung specimen seen via scanning electron microscopy. Backscattered electron image shows numerous particles in section.

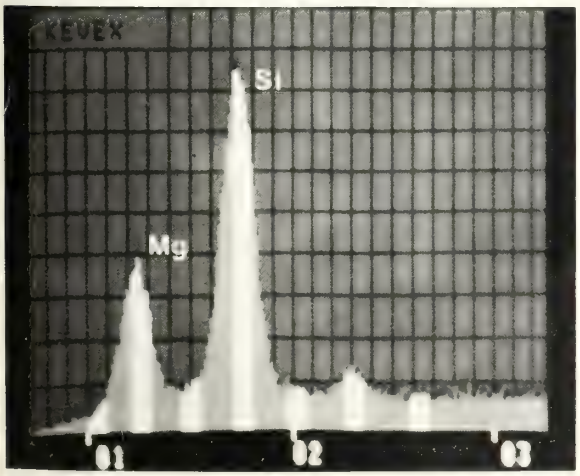

Figure 4.—Energy-dispersive x-ray analysis of particles seen on scanning electron microscopy. Peaks for magnesium (Mg) and silicone (Si) are consistent in ratio with talc (Mg_6 Si_8 O_{20} $[OH]_4$).

Discussion

Pneumoconiosis may develop in talc miners and other workers who are exposed to high concen-

Figure 5.—Photograph of a sputum smear with clusters of macrophages containing numerous birefringent particles. Also seen is a ferruginous body. (Iron stain, partially polarized, reduced from magnification ×300).

trations of talc dust for prolonged periods. This is characterized by a long symptom-free interval followed by the gradual development of cough and dyspnea and interstitial infiltrates with pleural plaques seen on chest roentgenograms. Pulmonary function studies usually have all the features of combined restriction, obstruction and a reduced single-breath diffusing capacity for carbon monoxide. This condition may progress to cor pulmonale and patients in whom it develops have a strikingly increased incidence of primary lung cancer.[5]

The clinical syndrome of lung disease caused by the inhalation of large quantities of cosmetic talcum appears to be indistinguishable from that of talc miner's pneumoconiosis. Nam and Gracey[6] reported autopsy findings of talc-induced lung disease in an asymptomatic patient who had a long-standing history of heavy talcum use. Wells and co-workers[7] reported a case of chronic talcosis of the lung diagnosed by open-lung biopsy in a patient who had a history of heavy talcum use as a dusting power. Fraser and Pare[5] reported a case of a young woman who had inhaled large quantities of talc from her hands during a postpartum depression. When seen, she had had dyspnea on exertion for several months and interstitial infiltrates were reported on chest roentgenograms. Diagnosis was established by open-lung biopsy.

In contrast to adults, infants who inhale massive doses of cosmetic talc have acute respiratory distress due to bronchial impaction and bronchiolitis obliterans.[9-11] Cruthirds and associates[12] reported a case of a ten-year-old child who had dyspnea, frequent respiratory infections and widespread interstitial infiltrates on chest x-ray films. This patient had aspirated talc at the age of two. Histologic examination of tissue obtained at open-lung biopsy showed extensive fibrosis, inflammatory infiltrates with giant cells and many crystals that were refractile under polarized light. Gould and Barnardo[13] reported a case of a seven-year-old girl who had acute respiratory distress after accidentally inhaling large quantities of powdered talc. Chronic bronchiectasis developed in this child and pulmonary function studies had all the features of both obstructive and restrictive defects.

Scanning electron microscopy with energy-dispersive x-ray analysis is ideally suited to the study of small specimens and the analysis of inhaled particulates that may be too small to see with a light microscope and too difficult to section for conventional transmission electron microscopy. Once located with a scanning electron microscope, regions of interest are analyzed using x-rays emitted by the specimen, which have characteristic energies for individual elements. The technique allows the detection of minute quantities of inorganic material in tissue sections (as little as 10^{-17} grams), samples a greater volume of tissue than transmission electron microscopy (approximately 50 times greater) and provides specific information concerning the composition of the detected inorganic dust particles.[8]

In conclusion, cosmetic talcum powder inhalation may be associated with acute or chronic talcosis of the lung. The clinical syndrome of lung disease in adults associated with the inhalation of large quantities of cosmetic talcum powder closely resembles that of talc miner's pneumoconiosis. Cosmetic talc pneumoconiosis should be considered in the differential diagnosis of bilateral pulmonary infiltrates. Diagnosis may be established by transbronchial biopsy using scanning electron microscopy and energy-dispersive x-ray analysis.

Summary

Cosmetic talcum powder is not generally considered to be a health hazard. We report a case of pulmonary talcosis due to the intentional sniffing of cosmetic talcum powder. Diagnosis was made by transbronchial biopsy using energy-dispersive x-ray analysis.

REFERENCES

1. Morgan WKC, Seaton A: Occupational Lung Diseases. Philadelphia, WB Saunders, 1975, pp 113-115

2. Russell RS, Merz RD, Silverston JN: The determination of respirable particles in talcum powder. Ed Cosmet Toxicol 1979; 17:117-122

3. Cosmetic talc powder (Editorial). Lancet 1977; 2(8026):1348-1349

4. Henderson WJ, Blundell G, Richards R, et al: Ingestion of talc particles by cultured lung fibroblasts. Environ Res 1975 Apr; 9:173-178

5. Fraser RG, Pare JAP: Diagnosis of Diseases of the Chest—Vol 2, 2nd Ed. Philadelphia. WB Saunders, 1978, pp 1189-1195

6. Nam K, Gracey DR: Pulmonary talcosis from cosmetic talcum powder. JAMA 1972 Jul 31; 221:492-493

7. Wells IP, Dubbins PA, Whimster WF: Pulmonary disease caused by the inhalation of cosmetic talcum powder. Br J Radiol 1979 Jul; 52(619):586-588

8. Abraham JL: Diagnostic applications of scanning electron microscopy and microanalysis in pathology. Israel J Med Sci 1979; 15:716-722

9. Pfenninger J, D'Apuzzo V: Powder aspiration in children—Report of two cases. Arch Dis Child 1977 Feb; 62:157-159

10. Motomatsu K, Adachi H, Uno T: Two infant deaths after inhaling baby powder. Chest 1979 Apr; 75:448-450

11. Brouillette F, Weber ML: Massive aspiration of talcum powder by an infant. Can Med Assoc J 1978 Aug 26; 119:354-355

12. Cruthirds TP, Cole FH, Paul RN: Pulmonary talcosis as a result of massive aspiration of baby powder. South Med J 1977 May; 70:626-628

13. Gould SR, Barnardo DE: Respiratory distress after talc inhalation. Br J Dis Chest 1972 Jul; 66:230-233

Refer to: Clark JM, Weeks WR, Tatton J: Drosophila myiasis mimicking sepsis in a newborn. West J Med 1982 May; 136:443-444

Drosophila Myiasis Mimicking Sepsis in a Newborn

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Figure 1.—Photograph of an eight-day-old infant with periorbital cellulitis with pustules.

MYIASIS IN THE NEONATAL period is a rare occurrence and almost exclusively found in tropical areas.[1,2] Its rarity and the clinical presentation of cellulitis and sepsis make the following case report intriguing. The supposed method of infestation and the responsible fly are likewise unique.

Report of a Case

A female neonate whose gestational, intrapartum and postpartum periods were unremarkable was seen by her physician at eight days of age because of increasing jaundice. A total serum bilirubin level of 16 mg per dl (normal up to 1 mg per dl) was found. Swelling and reddening around the right eye were also noted. During the following 24 hours, periorbital induration became severe and pustules appeared (Figure 1). Other pustules were noted in and behind the ears, on the checks, the palms of the hands and around the umbilicus. No pustules were found on the back or in the diaper area. Because of the history and physical findings, she was referred for evaluation and treatment of suspected sepsis.

On admission physical examination the infant was slightly irritable and was not in a toxic state. She weighed 2,700 grams, temperature was 36.0°C (96.8°F), respirations were 35 and pulse rate 140 per minute. In addition to the pustules and cellulitis there was mild omphalitis. The baby was noted to have a soft fontanelle, no hepatosplenomegaly, no bone or joint tenderness and a normal cardiorespiratory system. Cultures were obtained of blood, urine, cerebrospinal fluid and specimens from several pustules. Intravenous administration of ampicillin (150 mg per kg of body weight a day) and gentamicin sulfate (7.5 mg per kg a day) was begun. Gram stain of material from several pustules showed numerous polymorphonuclear leukocytes but no organisms. A complete blood count showed a hematocrit determination of 51 ml per dl and a leukocyte count of 15,800 per cu mm that differentiated to 2 percent band forms, 65 percent segmented forms, 4 percent eosinophils, 28 percent lymphocytes and 1 percent monocytes. Urine analysis and serum electrolyte and blood urea nitrogen levels were normal. Serum bilirubin level was 15.5 mg per dl total with a direct component of 0.6 mg per dl. Red blood cell morphology was normal, Coombs' test was negative and the reticulocyte count was 0.9 percent.

Within six hours after admission to hospital, movement was noted in the pustules. During the next two hours, 46 white larvae 3 to 4 mm long bored out of the pustules. These were collected and identified morphologically and by hatching as *Drosophila* larvae. As soon as all larvae were out of the epidermis, the cellulitis rapidly resolved and the pustules healed with no scarring. The hyperbilirubinemia dropped precipitously to 10 mg per dl over the first ten hours of hospital stay. X-ray films of the periorbital area showed no pathologic condition. All cultures were negative for pathogens at 48 hours and antibiotic medications were stopped.

Retrospectively, it was learned that the mother

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had spent a few days canning fruit and many fruit flies *(Drosophila)* had been in the house. The baby had received frequent attention during the canning process, with probable transfer of fruit juices to the exposed skin. The attraction of *Drosophila* to these fruit juices on the immunologically immature neonate's skin appeared to be the cause of the myiasis.[3]

The baby was discharged in good health after four days in hospital.

Discussion

An article discussing common methods of infestation with dipterous fly larvae has recently been published.[4] Topical infestation of ulcerated skin, ear canals and nostrils is well known. Some flies puncture the skin and deposit ova beneath the surface, while some lay their ova on the surface, which then hatch and burrow along hair follicles or directly through the skin. Other flies use insect vectors.[2]

The most common larvae causing myiasis in North America are the screwworm *(Cochliomyia hominivorax),* common cattle grub *(Hypoderma lineatum),* sarcophagid fly *(Wohlfahrtia vigil),* house fly *(Musca domestica)* and rabbit box fly *(Cuterebra cuniculi).*[5] *Drosophila* was not listed as a cause of dermal myiasis in the texts and articles reviewed. Myiasis in the neonate is not found in the medical literature of North America but is found in that of tropical areas of the world. The usual sites of infestation are the umbilical cord and foreskin.[1,2]

Summary

The presentation of an eight-day-old neonate with periorbital cellulitis, cutaneous pustules and hyperbilirubinemia normally signals sepsis. In this case the cause of the hyperbilirubinemia was not discovered and the problem rapidly resolved over the first ten hours of stay in hospital with increased fluid intake. The cellulitis and pustules proved to be due do *Drosophila* larvae infestation, a heretofore unlisted cause of myiasis.

REFERENCES

1. Székely R, Herreros C, Rojo M: Human umbilical myiasis by *Phaenicia sericata* in a newborn child. Bol Chil Parasitol 1975 Jan-Jun; 30:25-26 (Eng. Abstr.) (Spa.)

2. Bowe Douglas L, Amaro Trapaga E, Sotolongo Guerra F, et al: Otic myiasis in a newborn caused by Calliphoridae larvae. Rev Cubana Med Trop Havan 1977 May-Aug; 29:75-79 (Eng. Abstr.) (Spa.)

3. Schmidt LM: Topical dermatology therapy for the pediatrician. Pediatr Clin North Am 1978; 25:191-192

4. Preiser G, Lavell TE, Dorsey WF: Myiasis presenting as cellulitis of the cheek. Pediatrics 1979 Jul; 64(1):88-89

5. Domonkos AN, Arnold HL Jr, Odom RB: Diseases due to animal parasites, chap 20, *In* Andrews' Diseases of the Skin—Clinical Dermatology. 7th Ed. Philadelphia, WB Saunders, 1982, pp 526-580

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Myocardial Ischemia and Infarction Related to Recreational Cocaine Use

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ILLICIT USE OF COCAINE has been associated with toxic cardiovascular reactions including tachycardia, hypertension, ventricular arrhythmias and death.[1-4] We report the case of a patient in whom on separate occasions angina and a subendocardial myocardial infarction developed after intranasal application ("snorting") of cocaine.

Report of a Case

A 38-year-old healthy man was seen for routine medical care in October 1976. He had a 40-pack-year history of cigarette smoking. He said there was no personal or family history of myocardial infarction, hypertension, diabetes mellitus or hyperlipidemia. The patient was mildly overweight. His blood pressure was 120/80 mm of mercury and pulse rate was 68 per minute. On physical examination fundi were normal, pulses were full without bruits and there was no jugular venous distention. Cardiac examination was entirely normal as was the remainder of the physical examination. The results of all routine laboratory tests were within normal limits as were a random serum glucose test, thyroid function tests, chest roentgenogram and electrocardiogram.

In February 1977 the patient was admitted to hospital with dizziness and a feeling of heaviness in the left arm. A subendocardial anterolateral myocardial infarction was noted to be evolving on the electrocardiogram. The serum creatine phosphokinase level (CPK) was 310 IU per liter (normal, 2 to 83) with elevated MB bands. The

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patient recovered from his infarction and was subsequently able to walk three miles a day without difficulty.

He was free of symptoms until April 1980 when, after snorting approximately 0.5 grams of cocaine, chest and left neck pain, dyspnea, diaphoresis and anxiety developed. When seen in the emergency room, results of the physical examination were unchanged from 1976, except for a blood pressure of 152/98 mm of mercury and a pulse rate of 88 per minute. The electrocardiogram showed no abnormalities. The chest discomfort was relieved by nitroglycerin, a diagnosis of angina was made and the patient was sent home.

The patient abstained from cocaine use and had no more symptoms until October 1980 when, after snorting cocaine, he had substernal chest pressure radiating to the left arm, diaphoresis and dyspnea. On admission examination his blood pressure was 130/90 mm of mercury, pulse rate was 96 per minute and an S_4 gallop was noted. The hemoglobin level was 16.1 grams per dl and the chest roentgenogram was normal. An electrocardiogram showed sinus tachycardia at 110 per minute, normal intervals and axis and a new ST segment elevation with T wave flattening in leads II, III and aV_F. The pain resolved with the administration of nitrates and morphine sulfate. Evidence of a new inferolateral subendocardial myocardial infarction appeared on the electrocardiogram (Figure 1), associated with a serum CPK level of 87 IU per liter (normal, 2 to 83) with 13 percent MB bands. His fasting blood glucose level remained consistently more than 240 mg per dl and his blood pressure remained elevated at 140/90 mm of mercury. Before discharge he was treated with a weight reduction diet for obesity and diabetes and with diuretic medications for hypertension. The patient has since stopped using cocaine, is free of symptoms and has returned to work full time.

Discussion

Cocaine is derived from the leaves of *Erythroxylon coca* and other species of *Erythroxylon* trees native to Peru and Bolivia.[4] It was first introduced as a local anesthetic agent in 1884 and continues to be a popular agent because of its associated vasoconstriction property.[5] It affects the sympathetic nervous system by blocking reuptake of catecholamines at adrenergic nerve endings, thus potentiating both inhibitory and excitatory responses of sympathetically innervated structures to endogenous and exogenous norepinephrine and epinephrine.[4] Intravenous administration of cocaine produces a dose-related increase in heart rate and blood pressure,[1] reflecting increased central and peripheral sympathetic nervous system effects.[4]

This patient had both reversible and irreversi-

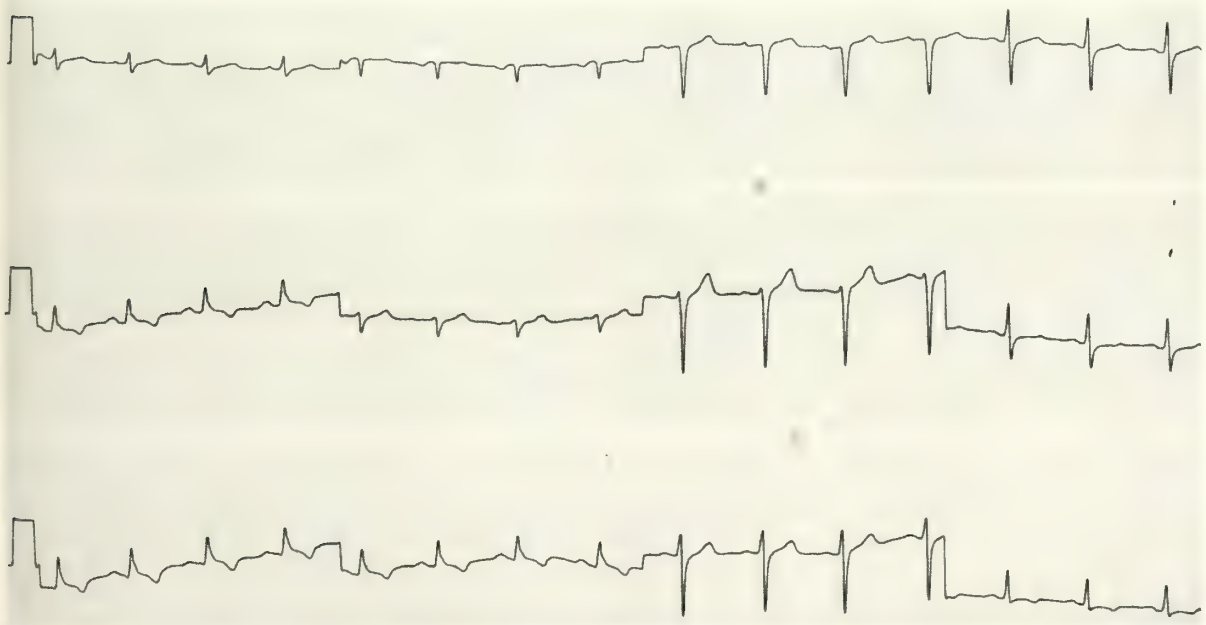

Figure 1.—A 12-lead electrocardiogram from October 1980 showing changes compatible with an inferolateral subendocardial myocardial infarction.

ble episodes of myocardial ischemia after snorting cocaine. Intranasal application of therapeutic concentrations of cocaine results in substantial blood levels of the drug within minutes that may last as long as six hours.[6] Independent of the underlying degree of the patient's fixed coronary artery lesions, the occurrence of myocardial ischemia after cocaine use may be due to either cocaine-mediated increases in heart rate, blood pressure and contractility or because of possible coronary artery vasoconstriction, both creating an imbalance between myocardial oxygen demand and supply.

Our patient said he was not using other prescription or illicit sympathomimetic agents that might have been potentiated by cocaine. He also said he was not taking agents such as reserpine or guanethidine that by catecholamine depletion might have enhanced receptor sensitivity to exogenous catecholamines.[5] The possibility that the cocaine was diluted with another sympathomimetic agent cannot be excluded.

In our urban medical center we are seeing increasing use of cocaine across all socioeconomic groups and age ranges. To our knowledge this case represents the first time myocardial ischemia and infarction have been reported in relation to recreational cocaine use.

Summary

Recreational use of cocaine has been increasing in various socioeconomic groups and age ranges. Illicit use of cocaine has been associated with tachycardia, hypertension, ventricular arrhythmias and death. We report the case of a patient with presumed underlying coronary artery disease in whom myocardial ischemia and infarction developed in relation to recreational cocaine use.

REFERENCES

1. Fischman MW, Schuster CR, Resnekov L, et al: Cardiovascular and subjective effects of intravenous cocaine administration in humans. Arch Gen Psychiatry 1976 Aug; 33:983-989

2. Benchimol A, Bartall H, Desser KB: Accelerated ventricular rhythm and cocaine abuse. Ann Intern Med 1978 Apr; 88:519-520

3. Wetli CV, Wright RK: Death caused by recreational cocaine use. JAMA 1979 Jun 8; 241:2519-2522

4. Ritchie JM, Greene NM: Local anesthetics, chap 15, *In* Gilman AG, Goodman LS, Gilman A (Eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 6th Ed. New York, Macmillan Publishing, 1980, pp 300-320

5. Smith RB: Cocaine and catecholamine interaction. Arch Otolaryngol 1973 Aug; 98:139-141

6. Van Dyke C, Barash PG, Jatlow P, et al: Cocaine: Plasma concentrations after intranasal application in man. Science 1976 Feb; 191:859-861

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Pneumococcal Pneumonia

TO THE EDITOR: I agree with Smith and Mann[1] in their call in the January issue for accurate data on rates of pneumococcal disease in community hospitals. Unfortunately, their article offers no useful contribution in this regard. In addition to the problem of patient selection, which is inherent in a retrospective analysis (and acknowledged by the authors), the critical reader is faced with a thoroughly inadequate description of the bacteriologic technique used during the period in question. What are "standard culture techniques" as applied to the isolation and identification of *Streptococcus pneumoniae?* Perhaps the board-certified pathologist mentioned in the article is unaware of the voluminous literature attesting to the colossal variability in isolation rates, which are dependent on the methodology utilized. For example, what volume of blood was cultured, using what media and what method? Were selective solid media used and were the specimens incubated anaerobically? Were the plates examined with the use of a stereo microscope?

These and other questions should be answered by the authors in order to make their report evaluable and useful in any comparative analysis.

STANLEY C. DERESINSKI, MD
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REFERENCE

1. Smith FE, Mann JM: Pneumococcal pneumonia: Experience in a community hospital. West J Med 1982 Jan; 136:1-5

* * *

TO THE EDITOR: Smith and Mann[1] reported that pneumococcal pneumonia, particularly bacteremic pneumonia, was uncommon in their patient population in Los Alamos, New Mexico. Several of their methods and results warrant comment.

First, I would question the validity of the data used to conclude that a "reasonable attempt" had been made to establish etiology. Respiratory secretions were cultured in 185 of 230 episodes (80.4 percent). However, as noted by the authors, no quality control was exerted either prospectively or retrospectively. Thus, in addition to the fact that culture of sputum does not distinguish colonization from infection,[2] the question of whether "sputum" specimens were truly representative of lower respiratory tract secretions cannot be resolved.

Second, definitive etiology can be established by culture of blood or lung aspirate. But blood cultures were done in only 95 of 230 patients (41.3 percent). No information is provided as to number of sets of cultures per patient. Since the bacteremia associated with pneumococcal pneumonia is not continuous, the number of times a blood culture is obtained will greatly influence the ability to detect its presence. Lung aspirate was obtained in only one instance.

Third, although review of outpatient use of antibiotics is mentioned in the methods, no data are provided in the results. Since the pneumococcus remains susceptible to most antibiotics that are prescribed in the outpatient setting, it is essential to know how often these drugs may have impaired the ability to detect the pathogen. A more favorable yield can be obtained by using an antimicrobial removal device, but this was not commercially available during the time of the study.

Fourth, the authors seem to conclude that pneumococcal pneumonia is uncommon in their community because of their geography—that is, rural rather than urban. I think a much more important aspect is the character of their patient population. A significant fraction of their community includes workers who are presumably healthy but seek acute medical care in Los Alamos. No data are provided about age distribution or underlying illnesses characteristic of the 17,000 to 25,000 people served by the hospital. In a recently reported retrospective review of bacteremic pneumococcal disease,[3] nature of the place of residence was irrelevant. There are many rural towns in western New York, and 60 percent of our patients come from such communities. The type of patient

served by a Veterans Administration Medical Center is the key determinant of our infection rate not the place of residence.

Fifth, in data presented by the authors, 25 patients had pneumococcal pneumonia, 11 of whom had blood cultures obtained; one was bacteremic. There is no statistically significant difference between this rate (9 percent) and the commonly reported 20 percent to 30 percent. In fact, if all other previously noted variables that may have produced negative cultures are considered, the positive yield of 9 percent seems quite consistent with expectations. But any conclusion extrapolated from these data is hazardous because of the small sample size.

Finally, readers should not conclude that this study supports the contention that pneumococcal pneumonia is restricted to urban or university hospitals. A larger, prospective study, as suggested by Smith and Mann, is needed. Both retrospective and prospective studies are ongoing at the Buffalo Veterans Administration Medical Center to determine incidence of disease among our patients. Data should also be obtained from other types of institutions before any conclusions can be drawn.

Vaccine efficacy and cost-effectiveness is also under evaluation in a double-blind, prospective, placebo-controlled trial at the Buffalo VA Medical Center. Although the recommendations for widespread vaccination have been questioned,[4] the report of Drs. Smith and Mann should not be used to discourage vaccination of high-risk persons in the rural setting.

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REFERENCES

1. Smith FE, Mann JM: Pneumococcal pneumonia: Experience in a community hospital. West J Med 1982 Jan; 136:1-5

2. Sanford JP, Pierce AK: Lower respiratory tract infections, *In* Bennett JV, Brachman PS (Eds): Hospital Infections. Boston, Little, Brown and Co, 1979, pp 255-286

3. Mylotte JM, Beam TR Jr: Comparison of community-acquired and nosocomial pneumococcal bacteremia. Am Rev Resp Dis 1981; 123:265-268

4. Hirschmann JV, Lipsky BA: Pneumococcal vaccine in the United States—A critical appraisal. JAMA 1981 Sep 25; 246: 1428-1432

* * *

The Authors Reply

TO THE EDITOR: We would like to submit the following in response to the letters of Dr. Deresinski and Dr. Beam.

Dr. Deresinski raises a question, which we well recognized, concerning the variability of isolation rates of *Streptococcus pneumoniae,* and Dr. Beam is concerned about the adequacy of pretreatment cultures. In all patients, blood specimens were obtained from two different sites and were taken one hour apart. Each specimen was inoculated into aerobic and anaerobic culture media. Some patients had additional cultures, but in a patient severely ill in the judgment of his attending physician, antibiotics were not withheld to obtain numerous sets of cultures. Once obtained, blood specimens are inoculated with 10 ml of blood into 100 ml of broth. Aerobic bottles contain tryptic soy broth and SPS (sulfite polymyxin sulfadiazine), and anaerobic bottles contain Columbia broth, SPS and sucrose. They are incubated in carbon dioxide. Blood cultures are routinely subcultured to chocolate agar plates at 24 and 72 hours, and culture bottles are incubated and examined for one week. Sputum specimens for culture were routinely inoculated on blood agar plates, chocolate agar plates and MacConkey agar plates.

Obtaining lung aspirate specimens is not practical in most community hospital settings, including ours, since even most board-certified, recently trained internists are not trained in this technique.

Patients who had been treated with antibiotics as outpatients were excluded from this study; most of these were less than 5 years old and were also excluded because of inadequate culture data.

Dr. Beam also raises a question about the Los Alamos population. The area served by Los Alamos Medical Center has a fairly standard population distribution for New Mexico: approximately 9 percent younger than 5 years old, 36 percent ages 5 to 19, 32 percent ages 20 to 44, 18 percent ages 45 to 64 and 5 percent older than 65. Chronic illnesses, for which most people are also treated at Los Alamos Medical Center, follow no unusual patterns. Our report included information on underlying diseases in patients with pneumococcal and nonpneumococcal pneumonia, and there were no substantial differences.

Dr. Deresinski commented on the variability in isolation rates of *S pneumoniae.* The difficulty of isolating *S pneumoniae* occurs in university and inner-city hospitals as well as in community hospitals. It seems unlikely, therefore, that the difficulty in isolation of pneumococcus is totally responsible for the lower incidence of bacteremic pneumococcal pneumonia in our community hospital.

It is very important to understand that we *do not* "contend," as suggested by Dr. Beam, that pneumococcal pneumonia is restricted to urban

or university hospitals. We certainly agree that data need to be obtained from other hospitals. Prospective studies in nonuniversity, nongovernment hospitals are difficult to do because of financial limitations, but we hope that such studies will be done in larger populations.

Finally, the recent US Public Health Service statement on pneumococcal vaccine use[1] appears to be a *backing off* from broad earlier recommendations which were based upon extrapolations from limited studies to large population groups.[2] We repeat our opinion that insufficient knowledge of pneumococcal disease epidemiology remains a barrier to optimal utilization of pneumococcal vaccine.

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REFERENCES

1. Immunization Practices Advisory Committee: Pneumococcal polysaccharide vaccine. Morbidity Mortality Weekly Rep 1981; 30:410-419

2. Hirschmann JV, Lipsky BA: Pneumococcal vaccine in the United States—A critical analysis. JAMA 1981 Sep 25; 246:1428-1432

More on the Dilemma of Nursing

TO THE EDITOR: Arthur E. Lyons, MD, raises a number of interesting points in his letter in the January 1982 issue.[1] His remarks can be divided into two major categories: nurses' salaries and inappropriate nurses' training. Unfortunately, it is the attitudes of physicians like Dr. Lyons on these issues that contribute to the continuing nursing crisis.

I agree with Dr. Lyons that salary is not the cause of the nursing crisis. However, low salaries and the lack of advancement are major factors why nurses are fleeing the profession. Nurses are required to work long shifts, usually beyond their regular 8-, 10- or 12-hour shifts, and often in understaffed situations. The long hours and stressful working conditions can take their toll both on the individual nurses and on their families. Higher salaries would not solve these problems but they would serve as earned compensation for the required responsibilities of hospital staff nurses.

Dr. Lyons' attitude about inappropriate nurse training is much more significant and perhaps a major reason why the nursing profession is in a crisis stage. It is true that many nurses are unhappy with their administrative responsibilities. This is understandable because most nurses become nurses to care for patients not to fill out forms. Unfortunately, the major way a nurse can advance is to assume more administrative responsibilities or go into academic settings. Physicians, like nurses, are not trained for and often dislike the administrative aspects of their profession. Indeed, this is the very reason that there are now graduate programs in hospital administration. Physicians could not and did not want to manage hospitals. Perhaps a similar profession will develop in the nursing area.

It is true that a major part of a nurse's day (or night) is devoted to bed making, answering bed calls, emptying bedpans and responding to doctors' orders. Too bad that when people are sick their bodily functions don't shut down, then none of us would have to worry about it. However, a doctor who believes that he has nothing to learn from nurses is sadly mistaken and dangerous to his patients. A doctor might spend only 15 or 20 minutes with a patient during the course of a 24-hour period. During this same period, a nurse will be with the patient virtually the entire time; this is categorically true in special care units. The nurse will know more about a patient's vital signs, fluid intake and output, and psychological well-being than many physicians could ever possibly know. Furthermore, a pediatric nurse contributes substantially to easing both the patient's and family's fears about the hospital stay and treatments.

Dr. Lyons also makes a point about nursing graduates' need for postgraduate preceptorship programs. Unless I am mistaken, I recall that medical school graduates are required to spend at least one additional year in training after they graduate before they can practice medicine on their own. Oh yes and isn't there something called a residency which can require five years or more of training after medical school before a physician is fully qualified for specialty practice? Unfortunately, residents, too, are often given responsibility for patient care before they are really ready. Indeed, medicine has recognized this by making interns and residents accountable to an attending physician. A few months is a remarkably short time for a nurse to learn to apply her new skills.

As a staff nurse on a pediatric floor, more than once I have had to mention or correct a physician's prescribed drug dosage, which if administered could place the child in jeopardy. Furthermore, along with the physician I would be legally and morally liable. I think this is equally as important as "pushing bedpans." A resident who

really wants to learn about the patient and treatment history will quickly establish a good working relationship with the staff nurse.

One final point should be made regarding the expanding technology in nursing. Most nurses see this as a necessary part of providing good patient care. Physicians, like nurses, must increasingly deal with advanced technologies for which they were not trained. A new professional who has become another important member of the health care team is the person who is trained to use these technologies—for example, in catheterization, radiology and radiation therapy, and on the hospital floor.

The nurses' profession like that of physicians is going through dramatic but necessary changes. There are many problems in the health care field and many reasons for these problems. Physicians must recognize, and fortunately many do, that nursing is a profession and nurses are part of the heath care team. The job is the profession, not vice versa. Dr. Lyons would do well to get another view on physician-nurse relationships.[2,3] Nurses, like physicians, are primarily concerned with delivering the best possible patient care. When Walt Kelley's character Pogo said, "We have met the enemy and he is us," he was not referring to any single group but to all of us. Physicians, nurses and all other health personnel are part of the problem but they are also the solution.

BETSY HAAS, RN
San Francisco

REFERENCES

1. Lyons AE: The dilemma of nursing (Correspondence). West J Med 1982 Jan; 136:70
2. Alper PR: What we have to do to help solve the nursing crisis. Medical Economics 1981 Jun; 8:73-79
3. Filardi GA: Rx for RNs: Job satisfaction. Ann Med News 1981 Oct 23; 4

* * *

TO THE EDITOR: The letter by Arthur J. Lyons, MD, in the January 1982 issue[1] contains some false assumptions. I would challenge Dr. Lyons to analyze these assumptions and refrain from stone throwing at other professions since his own glass house is as vulnerable and venerable.

Some of the assumptions are as follows:

(1) Registered nurses drop out of nursing faster than new graduates can enter the work force. (But, nursing has one of the highest retention rates of *all* female professions or occupations.)

(2) Linguistic usage of "they" and "their" in the letter assumes an adversarial relationship perceived and set up by the writer. (But, nursing continues to want collaboration and teamwork and may be frustrated by those whose present adversarial categories obstruct communication.)

(3) Education makes little difference in practice. (But, the medical educators are pushing for expanded curriculums and time limits in medical education.)

May I suggest that Dr. Lyons spend a workweek with a registered nurse and discern the highly sophisticated art and science of nursing where decisions can routinely mean life or death, recovering from illness or disintegration.

BARBARA L. NICHOLS, MS, RN
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REFERENCE

1. Lyons AE: The dilemma of nursing (Correspondence). West J Med 1982 Jan; 136:70-71

* * *

TO THE EDITOR: I wish to express my displeasure and disagreement with the letter written by Arthur E. Lyons, MD, "The Dilemma of Nursing," in the January 1982 issue.[1] The letter does not represent the views or attitudes of the majority of physicians. Attitudes such as those expressed by Dr. Lyons can only foster enmity between physicians and nurses. Furthermore, I think analysis of dilemmas within nursing rightfully belongs to nurses. We physicians have never taken kindly to outside criticism even though we have certainly faced dilemmas within our profession. Nursing deserves the same autonomy.

Most physicians (myself included) consider nurses to be partners in health care delivery. If Dr. Lyons is not familiar with this concept, I suggest he request a report of the proceedings of the conference on collaborative practice held February 4, 1982, in Sacramento sponsored by the Joint Practice Commission of the American Medical Association and the American Nurses Association. This commission funded a demonstration project of collaborative nurse/physician practice in four hospitals in the country. In brief, the four hospitals that participated in the project reported increased work satisfaction for physicians and nurses, improved nurse retention and recruitment, a climate of confidence and trust among nurses and physicians, and enthusiastic comments from patients about their care. Certainly this is the kind of practice that we want to encourage to foster a comprehensive approach to patient care.

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REFERENCE

1. Lyons AE: The dilemma of nursing (Correspondence). West J Med 1982 Jan; 136:70-71

Better Care at a Veterans Administration Medical Center

TO THE EDITOR: Although admitting offices at Veterans Administration medical facilities traditionally provide initial access and episodic care to eligible veterans, the passage of Public Law 93-82 in 1972 radically changed the delivery of care and permitted access to comprehensive, longitudinal and specialized outpatient care for these patients as well. This created considerable stress, not only for the professional staff but also for management.

In 1975 an ambulatory care service of three general internists was established at the Portland Veterans Administration Medical Center. It was then decided to develop a program in the admitting office that could effectively deliver excellent patient care and offer quality teaching. This was based on the premise that emergency units need general internists.[1] In order to accomplish this task it was necessary to obtain the sponsorship from the Medical Service at the Veterans Hospital and the University Department of Medicine, to integrate the teaching program with psychiatry and surgery, and to earn credibility with our patients, subspecialty colleagues, trainees, hospital management and nursing staff. In 1976 four full-time staff positions were converted to three academic faculty and two internal medicine senior resident positions. The following year the Veterans Administration central office granted stipends for five additional housestaff and a rotation for housestaff was initiated.

One of the faculty members in general medicine has ongoing administrative responsibility for the admitting office. For each rotation, there are two medical residents, one psychiatry resident, two interns each from surgery and medicine, one psychiatry intern, and one full-time faculty member from the section of general medicine. Each faculty member serves as attending physician on a three-week rotational basis. The commitment is more extensive than the traditional ward rotation for which all full-time faculty are responsible. Didactic sessions covering a wide spectrum of topics are scheduled daily. The chief of medicine conducts periodic rounds similar to those held on the wards.

The improvement in the delivery of patient care has been recognized by the faculty, nurses and administrative staff. Even the housestaff have become favorably impressed with their patient care and educational experiences in the admitting office. The once volatile issue of inappropriate and undesirable admissions has notably diminished although it still exists.[2,3] There is a waiting list for nurses and senior medical students who desire an assignment in the admitting office.

Three factors have contributed to the success of the program. The first is academic integration. The admitting office, no longer isolated, is a unit staffed by faculty and house officers, all of whom are affiliated with a department from the university. Second, the faculty have earned and maintained academic and professional credibility. Third, a critical mass of housestaff and faculty are available to operate an effective program.*

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REFERENCES

1. The emergency unit needs general internists (Editorial). SREPCIM Newsletter, Nov/Dec 1981, p 3
2. Girard DE, Watts WJ, Reuler JB, et al: The inappropriate admission, abstracted. Clin Res 1980 Feb; 28:32A
3. Papper S: The undesirable patient. J Chronic Dis 1970 May; 22:777-779

Nutrition in Geriatric Medicine

TO THE EDITOR: The December 1981 special issue on geriatric medicine arrived just as I was celebrating the beginning of my 60th year of life. I wonder how many besides myself noticed the obituary page—"In Memoriam." Out of the 18 physicians listed, 9, or one half were aged 60 or less. How depressing. Somewhere, there must be a lesson in this.

I was appalled, as usual, that once again, in these learned essays on aging, nutritional factors such as vitamins and minerals were totally neglected. In the whole issue there were three brief references to vitamins: vitamin B_{12} and folate in the article on anemia, and a very brief mention and immediate disclaimer of vitamin E, in the article "The Cellular Basis of Aging."

Why this disinterest, why this total disregard of readily available information? How can a magazine issue totally devoted to the problems of the aging totally disregard nutritional factors? Why?

Particularly distressing were the two articles on depression and dementia in the aged. The drugs recommended often turn elderly patients into zombies who sit all day, staring into space, defe-

cating and urinating on themselves. Can we really be so inhumane that we prefer these walking dead to an agitated but alive elderly patient? I wonder how many wondrous cures of these depressions and dementias could be achieved with supplementations of large doses of B vitamins and magnesium and other essential vitamins and minerals? We might truly be surprised.

The Medical Progress article "The Cellular Basis of Aging" in the same issue (pages 521-525) stated that "Epidemiological associations between exposure to environmental toxins, radioactivity or other factors that may alter cell function have not been established." So what. Does the author wish us to wait until we are all dead? What about Hiroshima and Nagasaki; did the atomic bomb not alter cell function? One large epidemiological study in Los Angeles by Goldsmith and co-workers several years ago clearly showed that mortality and morbidity in patients with chronic lung diseases was markedly decreased during major smog alerts when these patients were protected with fairly large doses of vitamin A, much larger than the usual 5,000 units per day, recommended by the Food and Drug Administration.

What about all the other evidence in the literature regarding vitamin and mineral supplementation, above the usual recommended doses and in addition to the so called "balanced diet"—which is the biggest hoax perpetrated by so called nutritionists, and has repeatedly been shown to be markedly deficient in many essential items. I would like to list but a few examples:

- Vitamin A—and its protective effect on skin, mucous membranes, its protection against toxins and infection, and its effect on eyesight. These are great areas of vulnerability in the aged.
- The B vitamins—their possible role in the prevention of arteriosclerosis and heart disease (niacin, pyridoxin, thiamin), their role in senile depression and dementia, Alzheimer's disease and other nervous disorders (thiamin, niacin, pyridoxin and others). One of the major causes of mortality and morbidity in rehabilitation centers is kidney stones. There is much research available, both in this country and in the rest of the world, showing that the incidence of calcium oxalate stones is greatly reduced by the prophylactic administration of pyridoxin and magnesium to patients with recurrence of this disorder. Yet, how many rehabilitation centers give these harmless supplements to their patients? *Primo non nocere.* Is it better to repeatedly operate on these patients, or to let them die, than to give them these inexpensive supplements?
- Vitamin C—and its controversial role in the many diseases of the aged such as cancer, heart disease and so forth.
- Vitamin E—and its possible role in the aging process of the cell, superoxidation, brown fat and the like, and in the prevention of arteriosclerosis and heart disease.

What about some of the important minerals, of which, according to some authors, more than 80 percent of our population is deficient?

- Magnesium—a major, essential mineral, essential in the prevention and treatment of such diseases as hypertension, arteriosclerosis, coronary artery disease, myocardial infarction, kidney stones and others (all major killers of our aging population). It is totally ignored by my learned colleagues, by our medical schools and leaders in research, in spite of a vast amount of research throughout the world, in spite of three international congresses on magnesium deficiency in the last ten years and in spite of major epidemiological studies done (such as the studies by Anderson and associates at McGill University[1] comparing the incidence and severity of myocardial infarctions in hard-water versus soft-water regions).
- Zinc—its role in wound healing, tissue integrity, heart disease, rheumatology, skin disorders, genital function and prostate disease (all major concerns of the aging).
- Chromium—its major role and importance in postmature, noninsulin dependent diabetes, its effect on cholesterol and triglycerides (again of great concern to the aged).
- Selenium and other important trace minerals —their effect on heart disease and other diseases of the aging.

I could go on and on. These are just a few areas that could have been studied and looked into by my learned colleagues. Instead, more and more drugs with all their side effects are studied, recommended and indiscriminately prescribed to our aging population.

I asked some questions at the beginning of this letter. Why this lack of interest, why this hostility toward an area that may have so much promise, not only for the aged but for our whole population? Many accuse us of selfish motives, of not really wanting our patients to get well, for reasons of greed. I cannot and will not believe this. But one cannot help but wonder sometimes why we

are so reluctant to look into these areas of research and promise.

BERNARD HORN, MD
El Cerrito, California

REFERENCE

1. Anderson TW, Neri LC, Schreiber GB, et al: Ischemic heart disease, water hardness and myocardial magnesium (Letter). Can Med Assoc J 1975; 199-203

* * *

EDITORS' NOTE—The editors asked two members of the Editorial Board to comment on Dr. Horn's letter. Their replies follow.

TO THE EDITOR: One cannot help but sympathize with Dr. Horn's concerns. If, as he suggests, the lack of vitamins and minerals in the diet were responsible for the host of diseases that afflict the geriatric population, the journal would have been neglectful indeed. Such does not appear to be the case, notwithstanding the flurry of articles in recent years in both the scientific and lay press which allude to a "possible role" of nutrient deficiency or imbalance in the causes of many "degenerative" diseases. Doubtless we still have much more to learn on this matter and it seems probable that, one day, a better understanding of nutrition will help to improve the health of the elderly. For the moment, however, it is "the coast dimly seen."

Despite much experimental work over many decades in both animals and humans, the significance of nutritional factors in most of the conditions cited by Horn remains conjectural. Thus, for example, it is unproved that aberrations in magnesium metabolism have any etiologic relationship to human hypertension, atherosclerosis, coronary artery disease, myocardial infarction or kidney stones. Similarly, while zinc seems essential for normal wound healing, deficiency of this element is likely an infrequent cause of delayed healing and neither zinc deficiency nor excess has been shown to play a role in heart, rheumatic or prostatic diseases in humans. While deficiency of the B vitamins can produce central nervous system disease, such deficiencies are not related to Alzheimer's disease or most other senile dementias.

While a modest increase in the quantity of vitamins and trace metals in the customary diet of geriatric patients may not be harmful, neither has it been shown to be beneficial. It is well known, moreover, that *larger* quantities of vitamins can be dangerous and, from animal studies, one would predict that excessive amounts of dietary "trace metals" are also inadvisable owing to the risk of metal-ion antagonism or imbalance.

Dr. Horn asks why there is a lack of interest in, even hostility toward, learning more about nutritional factors as causes of disease in the elderly. To the extent that such attitudes may exist, they can likely be attributed to a long history of overstatement, premature claims, disappointed expectations and faddism in what is historically a tedious and demanding field of scientific investigation.

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* * *

TO THE EDITOR: Thank you for asking me to comment on Dr. Bernard Horn's letter to the editor. He apparently reads the journal from cover to cover—at least he has the December number. And, your request has prompted me to read through that issue again.

It is a little difficult to correlate his observations on obituaries with the rest of his remarks. Perhaps you should give the cause of death and a dietary history on each of us who succumbs. It may be that a proper diet without alcohol and other drugs would reduce the deaths from auto accidents.

As one who is further along the chronological scale than Dr. Horn, I find myself entertaining a certain empathy with some of his basic statements. But instead of being depressed that one half of the individuals noted on the obituary page were age 60 or less, I rejoice that one half are over 60.

Perhaps more to the point in appraising the quality of the December issue would be to scrutinize how many of the essayists for that issue were over 60. I, not unlike Dr. Horn, became a bit depressed as I read what the authors have in store for me. I was struck by the lack of emphasis on prevention and the essence of pessimism in the learned essays more than in their neglect of "nutritional factors such as vitamins and minerals."

Dr. Horn's point about the disregard of nutritional factors has some validity. It is quite true that there is no article which shows the benefit of nutritional factors. What mention there is admits to a lack of knowledge—and this is distressing. On the other hand it may be pointed out that the subject has been covered at length in a special symposium of 60 pages on Nutrition in Medicine in February 1979 (volume 130, pages 93 through 152). It was given attention also in an article by Victor Herbert on "Nutrition Cultism" in the September 1981 issue.[1]

The significance and importance of dietary fac-

tors to health remain controversial. Writing in the journal of July 1981 on one of the more studied aspects of the problem, Hulley and his co-workers[2] reached the strong conclusion that "it is certain that dietary fats influence the level of serum cholesterol and it is highly likely that serum cholesterol is a cause of atherosclerosis in coronary artery disease." But in an editorial comment in the same issue, Hazzard[3] feared that "the clamor for a simple answer to a complex question such as this risks uncritical acceptance and unwarranted inappropriate application of the central conclusion of this analysis." The authors of both papers concluded that the decision to prescribe is a judgment that depends on the therapeutic philosophy of each clinician and on the particular needs of each patient.

Dr. Horn's angry diatribe against overuse of drugs is well taken. Some of us, nay, many of us, are guilty of giving drugs to keep patients quiet in institutions. Alas, I am not convinced that the dietary supplements Dr. Horn suggests would be as therapeutic as he seems to believe.

Finally, I find myself quoting Voltaire (although perhaps erroneously attributed to him) "I disapprove of what you say, but I will defend to the death your right to say it."

EDGAR WAYBURN, MD
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REFERENCES

1. Herbert V: Nutrition cultism (Informed Opinion). West J Med Sep 1981; 135:252-256
2. Hulley SB, Sherwin R, Nestle M, Lee R: Epidemiology as a guide to clinical decision—II. Diet and coronary heart disease (Nutrition in Medicine). West J Med 1981 Jul; 135:25-33
3. Hazzard WR: Diet, serum cholesterol and coronary heart disease—Has the dilemma been resolved at last? (Editorial). West J Med 1981 Jul; 135:52-53

Financial Aid for Medical Students

TO THE EDITOR: We are concerned with the dramatic increase in the cost of a medical education, which has been accompanied by drastic reductions in financial support for medical students. These reductions have occurred in both government and private loans, grants and scholarships. Several important points in this regard are as follows:

• Assuming no further inflation in the next four years, a student entering UCLA School of Medicine (for example) in 1981-1982 can anticipate spending $35,000 or more for four years in school. Two years ago, the corresponding figure was $26,000. For private California medical schools, the estimated cost for four years is $65,000.

• For the academic year 1980-1981, approximately 81 percent of the 630 UCLA medical students required financial aid to meet the above costs. Forty-two percent (or 265 students) applied to the school for financial aid and were determined to have financial need averaging $8,050 per student for the year. Another 39 percent (or 246 students) did not undergo a "needs analysis" by the school, but received financial assistance averaging $5,200 per student for the year, the funds being supplied mainly by federally guaranteed student loans.

TABLE 1.—*Annual Levels of Federal Spending for Financial Assistance to Students*

	Fiscal Year 1981 (million)	Fiscal Year 1982 (million)
Health Professions Student Loan	16.5	5.8
Exceptional Needs Scholarships	10.0	4.8
National Health Service Corps Scholarships	63.4	36.3

• On December 14, 1981, President Reagan signed into law the latest resolution that continues federal spending until March 31, 1982, at the annual levels shown in Table 1.

Further reductions may take place after March 31, 1982. The Reagan administration has also proposed that graduate and professional students be excluded from participation in the Guaranteed Student Loan Program (GSL), effective April 1, 1982. The Department of Education has already made this recommendation to the Office of Management and Budget. The GSL, along with the Health Professions Student Loans (HPSL) and the National Health Service Corps Scholarships (NHSC), have previously provided the bulk of financial assistance to students of low and middle income families.

• An alternative means of aid, the Health Education Assistance Loan (HEAL) program, is a private sector bank loan, at an interest rate equivalent to 91-day Treasury bills plus 3½ percent. The current HEAL interest is approximately 16 percent. A student borrowing $10,000 for his or her *first year* of medical school would repay $90,000 (principal plus interest) if payments were deferred until the end of residency (about 8 years) and then repaid over a 15-year period. Loans for the following three years of school would increase the debt far beyond this.

Failure to alleviate funding problems will cause serious difficulties. Some of the possible consequences are the following:

1. Students incurring nearly unmanageable debts may choose career specialties based on how

lucrative they are, and may need to practice in areas that yield higher fees and thus higher incomes, thereby adversely affecting physician distribution and health care cost containment.

2. Many bright, well-qualified and sincere students desiring medical education may be drawn toward other occupations merely because they cannot afford the cost of education.

3. Medical school classes may become homogeneous mixtures of the sons and daughters of the wealthy.

4. Students may take on outside employment during school, when valuable time is best spent studying medicine.

In summary, rapidly escalating costs of medical education, combined with dwindling sources of scholarships and low-interest loans, yield the prospect of serious problems in the training of young physicians.

Perhaps the best way to assist medical students in need of financial aid is via the establishment by the medical profession and by society of a substantial low-interest revolving loan fund at the medical schools. This fund would be administered by the financial aid offices, where documentation of financial need for students is maintained in confidential records. As with other loans, medical students could defer payment of such loans until after completion of their residency training, at which time the borrowed money would be returned to the loan fund over a permissible pay-back period (such as ten years). In the past, medical students have demonstrated an unusually responsible record in repaying loans with a very low default rate.

In an effort to preserve equal access to medical education and freedom of career choice, we request the serious consideration by physicians themselves and others in medicine of the establishment of a revolving low-interest loan fund for medical students.

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In Praise of the Triplicate

TO THE EDITOR: Not too many years ago it was part of my task as the Idaho Medical Association president to make the rounds of component societies pounding the drum for the various programs we had under way. One of these was the program requiring the use of "triplicate prescriptions" for controlled substances.

At first these prescriptions were greeted with considerable grumbling and foot-dragging. Even the members of our Board of Trustees were divided in their opinions. One of the newer members (I remember labeling him as a "young Turk") stoutly declared that the legislature and the State Board of Pharmacy were driving a wedge between doctors and patients.

At that time I, too, had a few misgivings that I could not, for obvious reasons, admit to my colleagues. It has been gratifying, therefore, to watch the program win unqualified approval in Idaho as the years rolled by.

In adopting the triplicate prescription concept Idaho was again following the lead of the state of California, where triplicate prescribing for narcotics has been required since 1939 and for all Schedule II drugs since 1981. Last year the state of Texas followed suit.

Can the success of this system of prescribing be documented in these two western states, California and Idaho, with their years of accumulated experience? In a personal communication, S. C. Helsley, chief of the California Bureau of Narcotic Enforcement, stated, "Based on information through undercover operations and by contacts with professional organizations and regulatory agencies we are very sure that the system has a very powerful deterrent effect."

Doyle C. Miner, executive director of the Idaho Board of Pharmacy, wrote, regarding the effectiveness of the program, "Although it is quite difficult to document, probably the best yardstick is the 70 percent decrease in Schedule II purchases in the pharmacies of the state. Another measure is the tremendous decrease in forgeries of Schedule II prescriptions."

It is my understanding that Oregon, Washington and Utah are looking into the possibility of adopting a triplicate program. I was pleasantly surprised to note that at the annual meeting of the Oregon Medical Association a representative of the Idaho Medical Association addressed the OMA delegates, expressing strong approval of the triplicate prescription system. And who was this physician who was pounding his drum? You guessed it: None other than that "young Turk" of another day, now the dynamic president of the Idaho Medical Association.

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Refer to: Martin AR: Common and correctable errors in diagnostic test ordering (Costs of Care). West J Med 1982 May; 136:456-461

Common and Correctable Errors in Diagnostic Test Ordering

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Diagnostic tests represent a significant percentage of medical costs. Knowledge of test ordering principles and a few testing strategies can significantly reduce unnecessary testing and costs. Awareness of the limitations of screening, less frequent monitoring of known abnormalities, reduced utilization of stat. *tests and test panels and better use of existing information will improve the efficiency and accuracy of diagnostic testing.*

LABORATORY and other diagnostic testing contribute substantially to the high cost of medical care.[1-5] It is likely that tests are overordered and that physicians can improve their test ordering skills.[4,6-11] In fact, some authors have questioned whether the increasing use of tests in the past two decades has brought about a real improvement in the quality of medical care.[12-16] Much of the discussion concerning the high cost of diagnostic testing has been focused on expensive technology such as computerized tomography, but, in fact, it has been shown that the repeated use of low cost tests contributes more to the hospital bill.[1,2,10] Routine clinical chemistry tests, hematologic, blood gas, bacteriologic and radiographic studies are all within the diagnostic armamentarium of virtually every physician. These diagnostic tests are numerous, and most are useful in a variety of clinical settings. Consequently, it is neither possible nor desirable to regulate directly their use by physicians. Efficient utilization is highly dependent on the skill of physicians at obtaining information about the patient's condition with a minimum of unnecessary ordering.

Studies in teaching institutions indicate that physicians in training can learn to modify and substantially reduce their test ordering if given instruction, focused on testing, that is reinforced over a period of time.[4,6-11,17,18] Changes occurred in some studies as a result of educational programs while others focused on physician motivation. Reductions in the ordering of tests by up to 50 percent have been achieved.[10] From review of studies of test utilization and from medical record review, it is possible to identify several common and correctable errors in the ordering of diagnostic tests. This paper describes patterns of overuse commonly observed and offers suggestions for changes that might be useful in medical practice. Table 1 summarizes the common errors in testing that will be discussed.

General Perspective

One of the concerns about controlling test utilization most commonly raised by physicians relates to its effect upon individual patients. Though one

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TABLE 1.—*Common Ways in Which Tests are Overordered*

Searching for asymptomatic disease
Too frequent monitoring of tests
Stat. testing
Ordering of test clusters
Failure to use available information
Outside information
Clinical setting
Other test data
Conditions of testing

may agree from a public policy perspective that reducing health care costs is useful, physicians are concerned with individual patients and are therefore reluctant to omit tests that have even a small likelihood of producing diagnostic information. However, this reluctance may not be as logical as it first seems. Since no test can perfectly separate patients with disease from normal (less than 100 percent sensitivity and specificity), every test introduces the possibility of false positive or false negative results. Multiplying the number of tests multiplies the opportunity for error. The possibility of being misled is particularly great if one tests for a disease that is very unlikely or uses a test that is not specific for the clinical situation.[19,20] Virtually any test, no matter how good, will produce more false than true positive results if the presence of disease is unlikely in the patient tested.[21] False positive results usually lead to more testing, sometimes to procedures that have significant morbidity,[22] and occasionally to labeling of healthy patients as diseased. Physicians can best serve patients by using clinical information to determine which diseases are most likely and then selecting the most sensitive and specific test for that clinical situation.[20]

Searching for Asymptomatic Disease

It is common when a patient is seen for the first time or admitted to the hospital that a battery of tests is ordered. As explained above, unless there are clinical clues to suggest that an abnormality may be present, one is testing an unselected population with low disease likelihood, and true positives will be vastly outnumbered by false positives occurring in the healthy population. It has been calculated that if a normal person has 12 independent laboratory tests, there is a 46 percent likelihood that at least one will be abnormal on the basis of chance alone.[23] In other words, many of those with positive screening tests are unlikely to have a real abnormality. In addition, the outcome of many of the diseases detected by screening is not appreciably changed by detection in the subclinical state. Recognition of these theoretical arguments favors screening only for diseases of significant likelihood and import.

The benefit of a routine battery of admission chemical and hematologic tests has been the subject of study. Korvin studied the results of an average of 20 admission tests on each of 1,000 patients.[24] In his study, only 83 new diagnoses were made in 77 patients. It was his impression that only one patient had long-lasting benefit from a new diagnosis and that 29 others had potential benefit but no evidence of follow-up of the abnormal test. Durbridge and colleagues, studying patients admitted to an acute general hospital, compared the outcome of 500 patients who had a battery of screening tests done on admission with the outcome of two control groups of 500 patients each, for whom tests were ordered only at their physicians' discretion.[25] The screening group had twice as many tests and 64 percent greater laboratory costs with no discernible benefits.

Some screening tests have become routine practice even though the evidence that they affect patient outcome is lacking. Routine yearly or biennial chest films are frequently ordered though evidence suggests that radiographs of the chest, even every six months, do not detect pulmonary carcinoma early enough to affect outcome[26,27] and though pulmonary tuberculosis can be screened for with a Mantoux test. Similarly, baseline electrocardiograms are frequently obtained on asymptomatic patients, though at least one study has questioned whether these baselines are of value subsequently.[28]

The most comprehensive assessment of the value of screening tests has been carried out by the Canadian Task Force on Periodic Health Examinations.[29] After their exhaustive review of literature, they were able to specify only three tests that they felt had good or fair evidence of benefit in an unselected population (mammography, Papanicolaou smear and stool test for occult blood). A small number of other tests were found to be useful in high-risk groups (gonorrhea culture, syphilis serology, Mantoux test, blood hemoglobin, protein, tests for Tay-Sachs disease and thalassemia and urine cytology). Thus, despite all of the tests that are advocated and done for

"screening," there is little evidence to support their value.

Too Frequent Monitoring of Tests

After obtaining an initial battery, tests that are abnormal or that relate to the disease process may be repeated in order to monitor the patient's progress. Studies have suggested that such repeat testing is overdone and that it is a major source of laboratory costs.[4,6,10] Despite a strong desire to follow the patient's progress, repeated use of diagnostic tests often yields little new information.

Unnecessary repeat testing may include obtaining serial, daily x-ray studies of the chest to monitor the progress of pneumonia or congestive heart failure. With congestive heart failure, radiologic improvement may lag up to 48 hours behind clinical improvement.[30] A study of patients with pneumococcal pneumonia suggested that radiologic clearing may take weeks and that six weeks is the appropriate interval between films to monitor progress.[31] Unless the patient is not improving clinically or there is question about the diagnosis, there seems little reason to obtain repeat films except to ensure that complete resolution has occurred. Frequent following of reticulocyte counts after starting therapy for anemia or frequent liver function tests in patients with hepatitis are also unlikely to produce useful information. Most healing processes require days to weeks, and follow-up tests obtained in two weeks are usually sufficient.

Serum electrolyte determinations are among the most frequently ordered tests in hospitals.[4] Unquestionably important, they are often overused. In my experience and that of others, it is not uncommon to see three or four sets of electrolyte studies obtained in a single day.[4] Except in the occasional patient in whom profound abnormalities are being corrected, sodium, chloride and bicarbonate values change sufficiently slowly that they require monitoring only every two to three days for patients receiving intravenous therapy. On the other hand, because of their potentially serious effect on the cardiovascular system and rapid changes with acid-base shifts, potassium and calcium levels may need monitoring every few hours, but only in selected patients.

It is routine to obtain serial enzyme determinations and electrocardiograms for patients admitted with suspected myocardial infarctions. Unfortunately, the standard set of three or four serial determinations is often done even when infarction is documented with the first set. If one wants to assess the severity of myocardial damage, following one enzyme—such as creatine phosphokinase or serum glutamic oxaloacetic transaminase (now known as serum aspartate aminotransferase)—is sufficient.[32]

Many physicians monitor diabetes mellitus in patients in hospital by obtaining blood glucose levels three and four times a day and giving insulin according to the level of blood sugar. This is clearly essential in patients who are acidotic, severely hyperglycemic, undergoing a surgical procedure or in the midst of major metabolic change. However, for most patients in hospital, fractional urine studies are an adequate means of monitoring diabetic control until they can return to normal activity and diet, and they cause considerably less discomfort. Blood glucose measurement can then be reserved for detailed adjustment of the insulin dose after discharge or for clarifying situations where the urine sugar tests consistently show maximal or negative readings.

Stat. Testing

All laboratories have procedures for expedited or rush processing of urgent tests, so-called *stat.* processing. The cost of tests processed *stat.* is considerably greater than normal for several reasons. Specimens must be set up and run separately instead of in the usual batch process. In some laboratories, the normal work must be interrupted to handle *stat.* requests while in others separate instruments and personnel must be available for processing *stat.* specimens. Results are usually phoned to the physician or in some way specially reported. Each step involves extra cost.

The volume of tests ordered *stat.* in many hospitals is surprisingly high. In some teaching hospitals 40 percent or more of chemistry tests may be ordered *stat.,* with some clinical units running as high as 80 percent (S. Cohen, MD, Director of Clinical Laboratories, University of California, San Francisco, personal communication). Information for some critically ill patients undoubtedly must be obtained immediately, but in many instances batches of tests for patients are ordered *stat.* when the results of only one or two are required immediately.

Unnecessary Ordering of Test Clusters

Tests are sometimes reflexly ordered in groups or clusters. Though multiple tests may be helpful

to confirm an abnormality or differentiate between diseases, they are seldom necessary in case finding or monitoring of a known abnormality. For example, many physicians order liver function tests that may include serum aspartate aminotransferase, serum glutamic pyruvic transaminase (now known as serum alanine aminotransferase), alkaline phosphatase, direct and total bilirubin, lactic dehydrogenase, total protein, albumin and prothrombin time when investigating the possibility of liver parenchymal disease. An aminotransferase determination alone is a very sensitive indicator of parenchymal disease and with the alkaline phosphatase will detect most significant liver derangements. Other tests can be obtained if there are abnormalities that need clarification.

Serum electrolyte determinations and the SMA-12 or SMAC battery are often repeated as a group though only one or two tests need to be followed. Although the difference in costs of running the entire battery is small, the amount charged by many laboratories makes it cheaper for the patient to have tests ordered individually if only one or two are needed. In addition, when multiple tests are run there are added costs of following up false positive results.

Similarly, a complete blood count and differential count may be useful at the time of a patient's admission, but too often the expensive, time-consuming differential count is repeated when all that needs to be followed is the automated hematocrit or leukocyte count.

Failure to Use Available Information

Failure to Obtain Outside Information

Any practicing physician knows that studies are frequently repeated because time has not been taken to obtain information from other institutions or physicians. In many instances, test results, radiographs and even pathologic specimens can be obtained if sufficient effort is made, and considerable expense and discomfort may be spared the patient. It is unfortunate for patients admitted to hospital to have tests repeated that were obtained in the ambulatory setting within days of the admission, often at the same laboratory.

Failure to Consider the Clinical Setting

In ordering a laboratory test or procedure, the question should always be asked, "Will the test result affect the patient's management?" A detailed search for metastatic lesions in a patient with carcinoma who is not a candidate for surgical removal of the primary tumor does not make much sense. Even when an operation is contemplated, extensive scanning may not be indicated. It has been shown in patients with adenocarcinoma or squamous cell carcinoma of the lung that brain, liver and bone scans are extremely unlikely to be positive in the absence of clinical or chemical signs of distant or widespread disease; yet the tests are frequently done.[33] Studies also suggest that in patients who are seen initially with metastatic carcinoma from an unknown primary site, multiple random radiologic and scanning procedures are likely to be expensive, fruitless and often misleading because of false positive results.[34,35] An appropriate "minimal" workup for patients with metastatic carcinoma from an unknown location could be a thorough history and physical examination, stool occult blood, urinalysis, chest x-ray and radiographic studies of organs manifesting specific dysfunction. An adequate biopsy specimen of the metastatic lesion should then be obtained for histologic examination and search for appropriate markers such as lymphocyte or germ cell markers, estrogen receptors or prostatic acid phosphatase, dependent on the histology. Two studies suggest that these tests will detect cases in which treatment needs to be altered.[34,35]

X-ray films of the lumbosacral spine are often ordered to investigate acute low back pain. In young persons with acute back pain the radiographs are usually unrevealing and rarely affect initial therapy.[36] Similarly, it is argued that radiographs to diagnose fractured ribs are unnecessary in patients whose clinical findings do not suggest compromised ventilation; an upper gastrointestinal series may not be needed in young patients with typical acid-peptic symptoms who respond to treatment.[36] For each of these clinical situations, radiographs can be obtained for patients who do not improve as expected.

Skull radiographs are commonly overused. They are not likely to yield new information in patients with headaches, dizziness or vertigo unless there are focal findings to be investigated.[37] Most tumors are not shown on a plain skull film, although a single lateral skull film to look at the pituitary fossa might be indicated in some patients. There are studies that indicate skull films should be carried out after head trauma only if there are specific historical or physical findings,[17] but it has

been difficult to get physicians to adopt these limits.[38]

Failure to Use Other Available Data

Historical information or other available test results can obviate the need for further testing. Platelet counts are not needed routinely before biopsy or operative procedures in patients with no history of bleeding and in whom an available blood smear has shown adequate platelets.[39] Eisenberg showed that a routinely ordered prothrombin time is extremely unlikely to be significantly abnormal in adult patients with no history of bleeding or evidence of liver disease.[40] It is common practice to order serum iron, iron binding capacity, serum B_{12} and folate levels for patients with anemia. Examination of the peripheral smear and reticulocyte count will narrow the possible types of anemia, and Griner has shown that red cell indices obtained from an automated complete blood count can be very helpful.[41] Anemic patients in hospital with a red cell mean corpuscular volume (MCV) less than 95 μm^3 had a 0.0011 probability of B_{12} or folate deficiency in Griner's study. Patients with a mean corpuscular hemoglobin (MCH) of greater than 30 pg had only a 3 percent chance of iron deficiency anemia.

Measurement of serum osmolarity is generally unnecessary unless there is reason to suspect an unmeasured osmotically active substance (mannitol, urea, alcohol). A doubling of the serum sodium value with corrections for elevated sugar (blood sugar/18 = osmoles) or urea nitrogen (urea nitrogen/2.8 = osmoles) is usually an accurate approximation of serum osmolarity.[42]

Failure to Account for the Conditions of Testing

Test results may have notably different meanings depending on the circumstances and timing of the tests. Hormone measurements are a significant example of this fact. Values for certain hormones such as cortisol, growth hormone and parathyroid hormone have such pronounced variation, depending on the time of day, meals, stress and other factors, that they are almost uninterpretable if studies are not done with knowledge of such conditions or with appropriate provocative or suppressive tests.[43] Similarly, there are no normal values for urinary electrolytes, and their interpretation is totally dependent on the patient's condition and intake. The urinary sodium determination is useful in trying to distinguish oliguria due to volume contraction from that due to acute renal failure.[44] It may also be helpful in evaluating hyponatremic patients suspected of having renal salt loss.[45] Urinary potassium measurement is helpful in a hypokalemic patient in whom renal potassium wasting is suspected.[46] Urinary chloride and bicarbonate are rarely clinically important.[46] Only specific tests needed for a given clinical situation should be obtained

There are several radiologic tests that are affected greatly by the conditions of testing. An intravenous pyelogram is not likely to produce visible images in an azotemic patient unless the radiologist is informed and uses a larger dye injection and tomography.[36] Liver scans, while helpful in evaluating liver size, often show focal defects due to scarring or fatty infiltration in patients with cirrhosis that are indistinguishable from tumor or abscess.[47] Perfusion lung scans can show changes indistinguishable from pulmonary embolus in patients with chronic obstructive pulmonary disease, congestive heart failure or pulmonary infection.[20] In each of the situations presented, knowing how the patient's condition will affect testing will allow one to select and interpret the tests correctly.

REFERENCES

1. Fineberg HV: Clinical chemistries: The high cost of low cost diagnostic tests, *In* Altman S, Blendon R (Eds): Medical Technology: The culprit behind health care costs? US Dept of Health, Education, and Welfare 144-65, DHEW publication No. PHS 79-3216, Government Printing Office, 1979

2. Moloney TW, Rogers DE: Medical technology—A different view of the contentious debate over costs. N Engl J Med 1979; 301:1413-1419

3. Freeborn DK, Baer D, Greenlick MR, et al: Determinants of medical care utilization: Physician's use of laboratory services. Am J Public Health 1972; 62:846-853

4. Griner PF, Liptzin B: Use of the laboratory in a teaching hospital: Implications for patient care, education and hospital costs. Ann Intern Med 1971; 75:157-163

5. Smith DM, Roberts SD, Cross TL: Components of the costs of care for medicine patients at an urban care center. Clin Res 1979; 27:284A

6. Dixon RH, Laszlo J: Utilization of clinical chemistry services by medical housestaff: An analysis. Arch Intern Med 1974; 134:1064-1067

7. Griner PF: Use of laboratory tests in a teaching hospital: Long-term trends: Reductions in use and relative costs. Ann Intern Med 1979 Feb; 90:243-248

8. Schroeder SA, Kenders K, Cooper JK, et al: Use of laboratory tests and pharmaceuticals: Variation among physicians and effect of cost audit on subsequent use. JAMA 1973; 225:969-973

9. Henderson D, D'Alessandri R, Westfall B, et al: Hospital cost containment: A little knowledge helps. Clin Res 1979; 27:279A

10. Martin AR, Wolf MA, Thibodeau L, et al: A trial of two strategies to modify the test-ordering behavior of medical residents. N Engl J Med 1980; 303:1330-1336

11. Eisenberg JM: An educational program to modify laboratory use by house staff. J Med Educ 1977; 52:578-581

12. Scitovsky AA, McCall N: Changes in the costs of treatment of selected illnesses: 1951-1967-1971 (Discussion Paper). San Francisco, University of California, San Francisco, Health Policy Program, 1975

13. Martin SP, Donaldson MC, London CD, et al: Inputs into coronary care during 30 years: A cost-effectiveness study. Ann Intern Med 1974; 81:289-293

14. Griner PF: Treatment of acute pulmonary edema: Conventional or intensive care? Ann Intern Med 1972; 77:501-506

15. Schroeder SA, Schliftman A, Piemme TE: Variation among physicians in use of laboratory tests: Relation to quality of care. Med Care 1974; 14:49-56

16. Daniels M, Schroeder SA: Variation among physicians in use of laboratory tests—II. Relation to clinical productivity and outcomes of care. Med Care 1977; 15:482-487

17. Bell RS, Loop JW: The utility and futility of skull examination for trauma. N Engl J Med 1971; 284:236-239

18. Marton KI, Sox HC: Comparison of two educational interventions for modifying house staff laboratory use. Clin Res 1981; 29:39A

19. Galen RS, Gambino SR: Beyond Normality: The Predictive Value and Efficiency of Medical Diagnoses. New York, John Wiley and Sons, 1975

20. Griner PF, Mayewski RJ, Mushlin AI, et al: Selection and interpretation of diagnostic tests and procedures. Ann Intern Med 1981; 94 (part 2):553-600

21. Vecchio TJ: Predictive value of a single diagnostic test in unselected populations. N Engl J Med 1966; 274:1171-1173

22. Schroeder SA, Marton KI, Strom B: Frequency and morbidity of invasive procedures: Report of a pilot study from two teaching hospitals. Arch Intern Med 1978; 138:1809-1811

23. Fleeson WP, Wenk RE: Pitfalls of mass chemical screening. Postgrad Med 1970 Sep; 48:59-64

24. Korvin CC, Pearce RH, Stanley J: Admissions screening: Clinical benefits. Ann Intern Med 1975; 83:197-203

25. Durbridge TC, Edwards F, Edwards RG, et al: Evaluation of benefits of screening tests done immediately on admission to hospital. Clin Chem 1976; 22:968-971

26. Boucot KR, Weiss W: Is curable lung cancer detected by semi-annual screening? JAMA 1973 Jun 4; 224:1361-1365

27. Weiss W, Seidman H, Boucot KR: The Philadelphia Pulmonary Neoplasm Research Project: Thwarting factors in periodic screening of lung cancer. Am Rev Resp Dis 1975; 111:289-297

28. Rubenstein LZ, Greenfield S: The baseline ECG in the evaluation of acute cardiac complaints. JAMA 1980; 244:2536-2539

29. Canadian Task Force on the Periodic Health Examination: The periodic health examination. Can Med Assoc J 1979 Nov 3; 121(9):1193-1254

30. Forrester JS, Diamond G, Chatterjee K, et al: Medical therapy of acute myocardial infarction by application of hemodynamic subsets. N Engl J Med 1976; 295:1356-1362

31. Jay SJ, Johanson WG, Pierce AK: The radiographic resolution of *Streptococcus pneumoniae* pneumonia. N Engl J Med 1975; 293:798-801

32. Coodley EL: Prognostic value of enzymes in myocardial infarction. JAMA 1973; 225:597-600

33. Hooper RG, Beechler CR, Johnson MC: Radioisotope scanning in the initial staging of bronchogenic carcinoma. Am Rev Resp Dis 1978; 118:279-286

34. Nystrom JS, Weiner JM, Wolf RM, et al: Identifying the primary site in metastatic cancer of unknown origin: Inadequacy of roentgenographic procedures. JAMA 1979; 241:381-383

35. Osteen RT, Kopf G, Wilson RE: In pursuit of the unknown primary. Presented at the Annual Meeting of the New England Surgical Society, Boston, Mass., 1977

36. Hall FM: Overutilization of radiologic examinations. Radiology 1976; 120:443-448

37. Bull JWD, Zilkha KJ: Rationalizing requests for x-ray films in neurology. Br Med J 1968; 4:569-570

38. Cummins RO, LoGerfo JP, Inui TS, et al: High-yield referral criteria for posttraumatic skull roentgenography. JAMA 1980; 244:673-676

39. Bell A, Neely CL: Smear platelet counts. South Med J 1980; 73:899-901

40. Eisenberg JM, Goldfarb S: Clinical usefulness of measuring prothrombin time as a routine admission test. Clin Chem 1976; 22:1644-1647

41. Griner PF, Oranburg PR: Predictive values of erythrocyte indices for tests of iron, folic acid and vitamin B_{12} deficiency. Am J Clin Pathol 1978; 70:748-752

42. Ferg PV, McCurdy DK: The hypertonic state. N Engl J Med 1977; 297:1444-1453

43. Isselbacher KJ, Adams RD, Braunwald E, et al (Eds): Harrison's Principles of Internal Medicine, 9th Ed. New York, McGraw-Hill, 1980, pp 444-445

44. Miller TR, Anderson RJ, Linas SL, et al: Urinary diagnostic indices in acute renal failure: A prospective study. Ann Intern Med 1978; 89:47-50

45. Leaf A: The clinical and physiologic significance of the serum sodium concentration. N Engl J Med 1962; 267:24-30, 77-83

46. Harrington JT, Cohen JJ: Measurement of urinary electrolytes: Indications and limitations. N Engl J Med 1975; 293:1241-1243

47. Klion FM, Rudavsky AZ: False-positive liver scans in patients with alcoholic liver disease. Ann Intern Med 1968; 69:283-291

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Medical Intensive Care in a Community Teaching Hospital

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The success of efforts at cost containment in medical intensive care units of community hospitals will ultimately depend on accurate assessments of their use by practitioners. This study analyzes 167 consecutive admissions to such a facility, 81 percent of which were supervised by physicians in practice in the community. The results suggest that a significant number of patients are admitted only for observation or conventional medical care, that a substantial proportion of resources is spent on the care of patients who die immediately and that there are few practitioners with enough experience in the daily operation of this facility to develop broad perspectives of its use. Physicians with specific training or more experience in intensive care medicine, such as full-time directors of medical intensive care units, should participate in the decisions about the allocation of the limited resources available to the critically ill.

ALTHOUGH A NUMBER of studies have dealt with the utilization of coronary care units,[1,2] respiratory care units[3,4] and general medical intensive care units,[5-9] few studies accurately portray the manner in which practicing internists treat their patients in the intensive care units of community hospitals. Studies of the units of university hospitals or publicly supported institutions are based on highly selected patient populations that may not be representative of those encountered in private practice. Medical care in Veterans Administration institutions or county facilities is often provided by resident physicians under the supervision of full-time faculty and may be influenced by limitations in the availability of beds or ancillary services. Moreover, in any of these settings the use of intensive care services may be influenced by research protocols. In view of the high prevalence of intensive care units in community hospitals,[10] we feel that careful study of the patterns of use of these facilities is warranted.

No single institution can completely reflect nationwide or even community-wide practice patterns but we felt that an accurate prospective evaluation of the practice of intensive care medicine in a large, community teaching hospital would be valuable. This report is an analysis of 167 consecutive admissions to a medical intensive care unit (MICU) designed for the care of patients with multisystem disease.

We chose to concentrate on four questions pertinent to effective use of intensive care: (1) Should demographic characteristics or functional

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ABBREVIATION USED IN TEXT

MICU = medical intensive care unit

status be used to select patients for admission to the unit? (2) How significant is the expenditure of resources for patients who die immediately? (3) Is there a subset of patients admitted to this unit who do not require its technologic sophistication? (4) Are there any practitioners with a sufficiently broad experience in the operation of this facility to properly assess its use?

Methods

Cedars-Sinai Medical Center is a 900-bed, acute-care, community teaching hospital serving the population of West Los Angeles. The Medical Center has a formal affiliation with the University of California, Los Angeles, School of Medicine, maintains a training program for 110 residents and fellows in internal medicine and has a complement of full-time physicians who are available for subspecialty consultation, including physicians who specialize in critical care medicine. The Department of Medicine operates a coronary care unit, a respiratory care unit and a general medical intensive care unit. Patients who suffer from cardiac or pulmonary diseases are usually admitted to the appropriate subspecialty units. The remaining patients with general medical illnesses who require intensive care are admitted to the eight-bed MICU and constitute the population of patients on which this study is based.

Patients

Although the Medical Center provides medical care to the indigent population of West Los Angeles, private patients account for approximately 95 percent of the admissions. Patients are referred for admission to the medical intensive care unit by any one of 370 private attending physicians on active status in the Department of Medicine. A small proportion of patients are admitted to the clinic service through the Medical Center's emergency room or ambulatory care facility. No formal restrictions exist for the admission of any of these patients to intensive care.

All adult patients entering the MICU during the three-month period, August 15 through November 15, 1979, were included in this study. Information about each patient was obtained by a review of the hospital record, by interview of the patient or by interview of the next-of-kin if the patient was physically or mentally incapacitated.

Physicians

Attending physicians retain the ultimate responsibility for the care of their private patients in the intensive care unit and are assisted by the house staff in all aspects of patient care. They also make decisions regarding transfer of their patients from the unit unless there is a shortage of beds. The full-time staff in the unit have educational and administrative responsibilities and advise the private physicians on selected aspects of patient care.

The subspecialty interest of an admitting physician was determined by examining the Department of Medicine records to see if that physician had been granted membership and privileges in a subspecialty division of the department. In most cases, only one physician's name appeared on the medical chart as the physician of record. If a patient was admitted by more than one physician and any one of these was a general internist, that patient was considered a patient of the general internist. In addition, if a patient was admitted by several subspecialists in unrelated practices, only the physician with the longest association with that patient was considered the physician of record and the others were classified consultants.

Laboratory Use

Six of the most frequently ordered laboratory tests were selected for a limited surveillance of laboratory use. These were the following: complete blood count, hematocrit, electrolyte panel, blood glucose, arterial blood gases and serum potassium. The number of laboratory tests performed in the unit was determined by counting the number of formal laboratory reports that had returned to a patient record from the time of admission to the unit to between 48 and 72 hours after the death or transfer of the patient.

Therapeutic Modalities

Monitoring and therapeutic modalities were determined by reviewing the cases with the house staff and by reviewing written orders. The number of transfusions was obtained by review of blood bank records.

Statistical Methods

Age differences between groups were compared using Student's unpaired *t* test. The number of

TABLE 1.—*Mortality by Age Group of 149 Patients in the Medical Intensive Care Unit*

Age Group (years)	*Subjects n=149 (percent)*	*Nonsurvivors n=40 (percent)*	*Mortality Within Group (percent)*
10-19	3 (2)*	0	0
20-29	12 (8)	0	0
30-39	11 (7)	1 (2.5)†	9
40-49	13 (9)	4 (10.0)	31
50-59	14 (9)	4 (10.0)	29
60-69	27 (18)	10 (25.0)	37
70-79	40 (27)	13 (32.5)	33
over 80	20 (19)	8 (20.0)	28

*The number in parentheses indicates the percentage of all subjects.
†The number in parentheses indicates the percentage of all nonsurvivors.

consultations, the number of laboratory tests and the rates of laboratory use were compared using the Wilcoxon two-sample test. Categorical variables were compared by chi-squared analysis.

Results

Patient Data

During the three-month interval, 149 patients were admitted on 167 occasions to the medical intensive care unit of Cedars-Sinai Medical Center. The mean age of the 149 patients was 62.7 years (range 18 to 95 years). The mean age of the 80 women (63.9 years) was not significantly higher than the mean age of the 69 men (60.8 years). Approximately 85 percent of these patients were white.

All patients were followed from entry to the unit until death or discharge from hospital. The duration of hospital stay ranged from less than a day to 303 days. The mean duration of observation for all patients was 19.0 days, for survivors 20.6 days and for nonsurvivors 14.9 days.

Of the 149 patients, 40 (26.8 percent of the total) died during their hospital stay. Of these 40 patients, 25 (62.5 percent) died in the intensive care unit and 15 (37.5 percent) died after transfer. The average age of the nonsurvivors (68.9 years) was significantly higher than the average age of the survivors (60.4 years; $P=.005$).

Table 1 illustrates the outcome of patients grouped according to decade of life. Only 1 of 26 patients less than 40 years of age died during the stay in hospital, a mortality of 3.8 percent. For the group of patients 40 years of age or older, the mortality was 31.7 percent, significantly higher than for the group less than 40 ($P=.008$). Elderly patients did not contribute an excess number of short-term hospital stays resulting in death. In fact, though patients more than 80 years of age comprised 19 percent of the total patient population, they accounted for only 20 percent of the deaths.

Of the total, 18 patients were admitted on 19 occasions with drug overdose. Because this group tended to be relatively young (mean age 43.2 years) and had an excellent prognosis (no deaths) despite the frequent use of major forms of therapy, the better outcome of the younger patient group might have been due to the inclusion of a significant number of overdose patients. Removing the

TABLE 2.—*Baseline Functional Status of Survivors and Nonsurvivors in Medical Intensive Care Unit*

	Survivors n=109 (percent)	*Nonsurvivors n=40 (percent)*
Employment Status		
Employed	25 (23.0)*	4 (10.0)
Full-time	20	3
Part-time	3	1
Status unknown	2	0
Unemployed	52 (48.0)	24 (60.0)
Elective retirement	24	11
Retirement forced by illness	19	11
Retirement, circumstances unknown	4	2
Recuperating from illness or temporarily unemployed	5	0
Student	2 (2.0)	0
Housewife	20 (18.0)	7 (17.5)
Employment status unknown	10 (9.0)	5 (12.5)
Residence		
Own home	84 (77.0)	32 (80.0)
Home of relative	10 (9.0)	5 (12.5)
Chronic-care facility	10 (9.0)	2 (5.0)
Visiting area	2 (2.0)	0
Information unavailable	3 (3.0)	1 (2.5)
Productivity		
Total self-care	78 (72.0)	26 (65.0)
Partial self-care	18 (16.5)	5 (12.5)
Unable to care for self	6 (6.0)	7 (17.5)
Information unavailable	7 (6.0)	2 (5.0)
Ambulatory Status		
Fully ambulatory	79 (72.0)	24 (60.0)
Partially ambulatory	14 (13.0)	5 (12.5)
Confined to wheelchair	1 (1.0)	4 (10.0)
Bedridden	8 (7.0)	6 (15.0)
Information unavailable	7 (6.0)	1 (2.5)
Mental Status		
Awake, alert with full intellectual capacity	51 (47.0)	18 (45.0)
Awake, alert but with deficiency in intellect or affect *not impairing* self-care or employment	28 (26.0)	11 (27.5)
Awake, alert but with deficit *impairing* self-care or employment	25 (23.0)	6 (15.0)
Lethargic or comatose	0 (0.0)	0 (0.0)
Status unknown	5 (5.0)	5 (12.5)

*The number in parentheses indicates the percentage of either survivors or nonsurvivors within each functional category.

overdose group from analysis, however, does not affect the difference in mortality between the younger and older populations.

The baseline functional status (Table 2) for each patient was carefully defined to determine whether the functional status was related to outcome. Of the 105 patients who claimed to have a regular occupation, only 28 percent were actively employed at the onset of the illness that prompted their admission to the MICU. Moreover, for the group of patients with a regular occupation who eventually died in the hospital, only 14 percent were employed. Of those patients who were unemployed and for whom we have adequate information, about half had been permanently disabled by preceding illnesses. Only 7 percent of the unemployed had any intention of returning to work on their return to baseline health. Despite the low rates of employment, most of these patients were leading reasonably independent lives at home.

Physicians

Private patients accounted for 81 percent of all admissions during the three-month period of study. Table 3 shows the subspecialty interest of the physicians who admitted private patients to the MICU. General internists were responsible for 18 percent of these admissions. No subspecialty group predominated, either in terms of admissions or patient-days. Cardiologists admitted the greatest number of private patients, but they were col-

TABLE 3.—*Physicians of Record for 135 Private Admissions to Medical Intensive Care Unit*

	Survivors	Non-survivors	Totals
General internists	19	5	24
Cardiologists	28	5	33
Pulmonary physicians	1	0	1
Nephrologists	15	7	22
Hematologists/oncologists	6	7	13
Endocrinologists	5	5	10
Gastroenterologists	12	7	19
Neurologists	2	1	3
Rheumatologists	6	2	8
Infectious disease physicians	2	0	2
TOTALS	96	39	135

TABLE 4.—*Consultations Requested by the Principal Physician in 135 Private Admissions*

Number of Consultations	Number of Admissions in Which Consultants Were Used Number (percent)	Number of Consultants Used
Survivors (96 admissions)	58 (60)	108
Nonsurvivors (39 admissions)	30 (77)	84
All patients (135 admissions)	88 (65)	192

Type of Consultation

Medical		Surgical		Other	
Cardiology	3	General surgery	28	Dermatology	2
Pulmonary	14	Vascular surgery	19	Gynecology	2
Nephrology	17	Orthopedic surgery	3	Psychiatry	2
Hematology/oncology	11	Head & neck surgery	2	Records unavailable	9
Endocrinology	7	Urology	4		
Gastroenterology	22	Neurosurgery	8		
Neurology	11	Otolaryngology	5		
Rheumatology	1	Plastic surgery	1		
Infectious disease	20	TOTAL: 192			
Intensive care	1				

TABLE 5.—*Patterns of Use of Medical Intensive Care Unit (MICU) by Survivors and Nonsurvivors*

	Survivors	Non-survivors
General		
Number of patients	109	40
Number of admissions	120	47
Average duration of stay in MICU	3.6 days	4.8 days
Percentage of hospital stay spent in MICU	12.6%	27.1%

Day	Number of Deaths n=40	Cumulative Percentage (%) of All Deaths
Day of Death for 40 Nonsurvivors from Date of Entry to MICU		
1	6	15.0
2	5	27.5
3	3	35.0
4	5	47.5
5	1	50.0
6	2	55.0
7	0	55.0
8	2	60.0
9	3	67.5
10	1	70.0
13-119	12	100.0

Day	Number of Transfers n=120	Cumulative Percentage (%) of All Transfers
Day of Transfer From MICU for 120 Admissions in Which Patient Survived		
1	43	36.0
2	29	60.0
3	10	68.0
4	17	82.5
5	5	87.0
6	4	90.0
7	4	93.0
8	2	95.0
9	0	95.0
10	1	96.0
12-24	5	100.0

lectively responsible for only 20 percent of all admissions.

Table 4 lists the consultations that were obtained by principal physicians for their private patients in the MICU. At least one consultation was requested in 65 percent of the 135 private admissions to the unit. Although a significant proportion of both survivors and nonsurvivors were not seen by any consultant during their stay, a principal physician often used the services of more than one consultant for those patients who required subspecialty expertise. In this group of patients, those who died were seen more frequently (an average of 2.8 consultations per admission) than survivors (an average of 1.9 consultations per admission; $P = .001$). These averages exclude the participation of full-time physicians, who were available for advice on selected aspects of patient care.

Utilization of Resources

The first section of Table 5 compares MICU use for survivors and nonsurvivors. A total of 28 percent of admissions and 33 percent of patient-days in MICU were devoted to the care of patients who died.

Several observations suggest that patients admitted to this facility remain at substantial risk of dying despite intensive supportive care, even when such care is given for protracted periods of time. The second section of Table 5 notes the day of death for the 40 nonsurvivors from the date of entry to the MICU. Although half of this group had died by the fifth hospital day, deaths also occurred among those who had received uninterrupted care for periods of up to four months. Patients who died after their transfer from the unit constituted 38 percent of the entire nonsurvivor group and the in-hospital mortality of patients who were transferred was 12 percent. The high rate of death for these patients undoubtedly reflects the practice of some physicians who transfer their moribund patients to the medical wards.

The third section of Table 5 lists the day of transfer for patients who survived their hospital stay. Of the survivor group, 33 percent had been transferred within 24 hours and almost two thirds of the entire group of survivors had left the MICU within 48 hours. Such data suggest that a large number of patients were admitted to the unit who required only brief observation or supportive care

TABLE 6.—*Diagnostic Procedures Done on Survivors and Nonsurvivors in the Medical Intensive Care Unit*

	No. of Admissions in Which Procedure Was Done	
	Survivors n = 120	*Non-survivors n = 47*
Invasive Monitoring Procedures		
Swan-Ganz catheter	16 (13)*	22 (47)
Arterial line	34 (28)	31 (66)
TOTAL	50	53

*The number in parentheses indicates the percentage of admissions in which procedure was done.

	Survivors—n = 120			*Nonsurvivors—n = 47*		
	Total Number	*Average*	*Range*	*Total Number*	*Average*	*Range*
Routine Laboratory Procedures						
Electrolytes	537	4.9	0-30	292	7.3	0-31
Separate serum potassium	284	2.6	0-36	190	4.8	0-34
Blood glucose	581	5.3	0-81	403	10.1	0-99
Complete blood count	790	7.2	0-56	377	9.4	0-34
Separate hematocrit	38	0.3	0-4	37	0.9	0-16
Arterial blood gases	1,056	9.7	0-112	891	22.3	0-104

	Survivors	*Nonsurvivors*
Analysis of Laboratory Procedures		
Total number of routine tests	3,286 (60)*	2,190 (40)
Average number of tests per patient	30.1	54.8
Frequency of routine tests	8.4/patient-day	11.5/patient-day

*The number in parentheses indicates the percentage of all routine tests.

before they were deemed sufficiently stable by their physician for transfer.

The routine and invasive monitoring procedures used during the study period are shown in Table 6. Of patients who died after intensive care therapy, 47 percent had Swan-Ganz catheter monitoring, a frequency that was almost four times greater than in the group of patients who survived. Arterial pressure monitoring was more commonly done, both in survivors (28 percent of admissions) and in nonsurvivors (66 percent). Overall, about half of all invasive monitoring procedures were done on nonsurvivors.

Routine laboratory procedures were monitored prospectively in the study group during their stay in the MICU. The numbers reported in the second section of Table 6 show what should be considered minimal estimates of six commonly ordered tests, since they do not include lost samples or reports that had been even slightly delayed in returning to the chart. Based on this survey, an eight-bed medical intensive care unit will generate 22,000 determinations of the six most commonly ordered laboratory tests per annum, 40 percent of which will be done for patients who will not survive their hospital stay. Nonsurvivors had more tests performed than survivors (54.8 per patient versus 30.1 per patient, respectively; $P = .0002$) and they were done more frequently (11.5 per day versus 8.4 per day, respectively, $P = .0003$). There was no correlation between the frequency of laboratory testing and length of stay for either group.

Several additional patterns of laboratory use are notable. The most commonly ordered test during the period of study was arterial blood gases. The average nonsurvivor had 22.3 determinations done before death and the average survivor had 9.7 determinations done before transfer. Of the 1,947 blood gas determinations done, 1,429 (73 percent) were obtained on 61 occasions in which the patient was intubated, an average of 23 per intubation. Also of note is the large number of so-called panel studies (complete blood counts or electrolyte panels) compared with the number of more specific determinations (such as hematocrits or separate serum potassiums).

The therapeutic modalities used on these patients are listed in Table 7. Because intensive

TABLE 7.—*Therapeutic Modalities Used for Survivors and Nonsurvivors in the Medical Intensive Care Unit*

	Number of Admissions Therapy Was Used n = 167 (percent)	*Number of Nonsurvivor Admissions Therapy Was Used n = 47 (percent)*
Procedure		
Cardioversion (elective)	3 (2.0)	2 (4.0)
Pacing catheter	3 (2.0)	2 (4.0)
Intubation	61 (36.5)	27 (57.0)
Tracheostomy	4 (2.0)	1 (2.0)
Mechanical ventilation	51 (30.5)	24 (51.0)
Positive end-expiratory pressure	6 (4.0)	4 (8.5)
Chest tube	3 (2.0)	1 (2.0)
Peritoneal dialysis	6 (4.0)	4 (8.5)
Hemodialysis	12 (7.0)	6 (13.0)
Plasmapheresis	3 (2.0)	0
Balloon tamponade of esophageal varices	4 (2.0)	3 (6.0)
Vasopressin (Pitressin) infusion for gastrointestinal bleeding		
Peripheral	9 (5.0)	4 (8.5)
Selective arterial	1 (0.6)	0
Sodium nitroprusside	15 (9.0)	8 (17.0)
Vasopressors	41 (24.5)	24 (51.0)
Dopamine hydrochloride	36 (22.0)	21 (45.0)
Isoproterenol hydrochloride (Isuprel)	7 (4.0)	5 (11.0)
Norepinephrine bitartrate (Levophed)	12 (7.0)	11 (23.0)
Other	3 (2.0)	3 (6.0)
Arterial infusion of chemotherapeutic agents	1 (0.6)	0
Hemoperfusion	2 (1.0)	0

	Survivors			*Nonsurvivors*			*Percentage (%) of Units to Nonsurvivors*
	Units	*Patients*	*Average Per Patient*	*Units*	*Patients*	*Average Per Patient*	
Transfusion of Blood Products							
Red cells	177	34	5.2	114	18	6.3	39
Fresh frozen plasma	122	13	9.4	60	10	6.0	33
Platelets	49	4	12.2	83	5	16.6	63
Cryoprecipitate	20	1	20.0	0	0	0	0
Plateletpheresis	0	0	0	3	2	1.5	100
Leukapheresis	0	0	0	7	3	2.3	100
TOTALS	368	52		267	38		

Survivors	*Nonsurvivors*	*Totals*
Frequency of Admissions for Conservative Therapy		
56/120 (47%)	9/47 (19%)	65/167 (39%)

observation, intensive nursing care and parenteral administration of fluids or some medications were difficult to monitor and to quantitate, these therapies were not specifically assessed during the study period. Of the specific modalities surveyed, no single mode of therapy was used on more than 5 percent of admissions except for intubation (36.5 percent), mechanical ventilation (30.5 percent), vasopressors (24.5 percent), sodium nitroprusside therapy (9 percent) and hemodialysis (7 percent). Hence, though a large number of therapeutic modalities were available to the patients admitted to this unit, many were rarely used.

When transfusions were needed, a large number of units were usually required. Almost half of all conventional units of blood products and all of the plateletpheresis and leukapheresis transfusions were given to those patients who died.

We were most interested in the number of patients who were admitted to intensive care in whom conservative therapy was administered. This investigation was prompted by our observation of a substantial number of patients who were transferred from the unit after a very brief period. For the purposes of this study, we defined conservative therapy as that which was given to a patient who did not require Swan-Ganz monitoring and that consisted of none of the surveyed therapeutic modalities except for transfusions of four units or fewer of red cells, platelets or fresh frozen plasma.

Table 7 shows that, based on these criteria, about 40 percent of admissions to intensive care were for patients who required only conservative therapy. Most interestingly, 19 percent of nonsurvivors received only conservative care when they were in MICU. A review of the records for these nine patients revealed that five were admitted for terminal malignancy, three for irreversible neurologic injury and one for hepatic encephalopathy.

Mortality may be favorably influenced by the inclusion of patients with drug overdose or by the practice of admitting patients who need only observation or conservative therapy. Because these patients have an excellent prognosis, their inclusion in the analysis of therapeutic outcomes may distort the results of intensive care therapy given to patients with more protracted or more serious medical problems. When the overdose group and the conservative therapy group are removed from analysis, the inpatient mortality for patients who were treated with any of the surveyed therapeutic modalities rose to 44 percent.

Discussion

This study has several features that help to define the manner in which intensive care medicine is practiced in this community:

- Most of the admissions were of private patients (81 percent).
- Any one of 370 practicing internists was eligible for admitting patients to the MICU.
- Most of the patients were drawn from the immediate community, and half of the study group was admitted through the emergency room of this hospital.
- No arbitrary admission criteria were in effect during the study, and policies mandating the transfer of the hopelessly ill were not enforced.
- No research protocols were in use during the study period.
- There were no significant limitations in ancillary services.
- Although aided by full-time physicians and house staff, the private practitioners remained directly responsible for their patients' care in the unit.

The outcome of patients admitted to the intensive care unit of our institution was poor despite the commitment of substantial resources to their care. The prognosis was especially poor for those patients who required any of the major forms of intervention available in the unit. Studies of intensive care intervention in other clinical settings[5,7,9] have also yielded disappointing results. Because we were interested in developing strategies that would promote more effective use of the MICU, we also sought the answers to more specific questions in this study.

Should age or functional status be considered in selecting patients for admission to the medical intensive care unit? The typical patient admitted to the MICU of this institution is most likely to be elderly and either retired from professional activity or disabled by underlying illness. It would be unreasonable to expect that intensive care therapy in this situation would restore a large number of patients to an economically productive status. Most of them were able to maintain their own homes, however, had normal or minimally impaired mental status, were reasonably self-sufficient and were ambulatory. These observations

suggest that many of our patients were leading relatively independent lives even in the absence of gainful employment.

The use of admission criteria based on age or functional status does not appear to be justified in this setting. Age alone did not distinguish a population at excessive risk for early death among the large number of patients over 40 years of age. In addition, diminished physical or mental capacity was a poor predictor of inpatient mortality, and restrictions based on such debility would have affected only a small fraction of patients admitted to this facility.

How significant is the expenditure of resources for patients who die? Our study suggests that the greatest expenditures of manpower and resources are often made for patients with the poorest prognoses. Although nonsurvivors represented 26.8 percent of the total study group, they accounted for 33 percent of the patient-days in MICU, 40 percent of routine laboratory tests, 56 percent of the invasive monitoring, 44 percent of the consultations and about half of all blood products and therapeutic modalities. In addition, patients with fatal outcomes had the highest rates of laboratory use. Excessive consumption of resources by patients with the poorest prognoses is a phenomenon that has been observed by others.[11,12]

Several aspects of laboratory use may have implications for cost containment. We found that arterial blood gases are the most commonly ordered diagnostic test and that the majority of such determinations are done on patients receiving ventilatory support. A dramatic increment in the use of this test was also observed by Griner[8] when an intensive care unit was used for the treatment of pulmonary edema. The development of a simple and noninvasive method for monitoring gas exchange may have a significant impact on the frequency of invasive arterial procedures and on the overall costs of laboratory testing in the MICU.

Do all the patients admitted to the unit use the resources available to them? We were most intrigued by the large number of admissions in which no specific therapeutic modality was detected by our screening procedures or in which the patient was transferred after a brief stay. We suspect that a substantial proportion of patients admitted to the MICU need only very abbreviated periods of monitoring or intensive nursing care. This observation is even more important when one considers that this institution maintains several other units specifically for the monitoring of cardiac and postoperative patients. Thibault and co-workers[9] have noted similar patterns of use in a general medical intensive care unit.

These data suggest that, when confronted with only two options in the level of care (conventional versus intensive care), many practitioners will admit patients who require intermediate levels of care to the MICU. Perhaps this demand for intermediate care can justify the development of areas where expenditures for more sophisticated equipment would be unnecessary and for which the hospital can be reimbursed at intermediate levels. We have also found that many of the available therapeutic modalities were rarely used. In these circumstances, it would be inefficient to equip every MICU bed with the capacity to administer every form of therapy.

Who should be responsible for the allocation of limited resources in the medical intensive care unit? Faced with limitations of such valuable resources, we have found it difficult to decide on the person who should bear this responsibility. Ideally, such an individual should be able to assess each patient's needs when critical illnesses develop, be conversant in many different diseases and be able to compare relative prognoses of patients with different diseases who are followed by subspecialists with diverse clinical interests. Our study suggests that by the time a patient in this community reaches the terminal stages of his illness and is admitted to our ICU, very few general internists remain the physician of record. In addition, both general internists and subspecialists require many consultants for the multitude of problems that apparently exceed the capacity of the primary physician to handle. Finally, it appears that no single practitioner or group of practitioners cares for a sufficient number of critically ill patients in this unit to gain a broad overview of their relative prognoses. We believe that full-time physicians have more expertise in the allocation of intensive care resources by virtue of their greater experience in this setting.

Conclusion

It appears that the following conclusions can be drawn:

- In the setting of a large, community teaching hospital, arbitrary criteria for admission to the medical intensive care unit are inappropriate.
- There is a very significant expenditure of resources for patients who will die shortly.

- There is a large subset of patients admitted to the unit who do not need its technologic sophistication.
- Physicians with more expertise in the field of critical care medicine should participate in decisions regarding the use of these facilities.

Our conclusions suggest that patient prognosis, physician involvement and use of intensive care facilities deserve much closer scrutiny.

REFERENCES

1. Bloom BS, Peterson OL: End results, cost and productivity of coronary care units. N Engl J Med 1973 Jan 11; 288:72-78

2. Peterson OL: Myocardial infarction: Unit or home care? Ann Intern Med 1978 Feb; 88:259-261

3. Rogers RM, Weiler C, Ruppenthal B: Impact of the respiratory intensive care unit on survival of patients with acute respiratory failure. Chest 1972 Jul; 62:94-97

4. Davidson IA, Bargh W, Cruickshank AN, et al: Crush injuries of the chest: A follow-up study of patients treated in an artificial ventilation unit. Thorax 1969 Sep; 24:563-567

5. Spagnolo SV, Hershberg PI, Zimmerman HJ: Medical intensive care unit—Mortality rate experience in large teaching hospital. NY State J Med 1973 Mar 15; 73:754-757

6. Callahan JA, Spiekerman RE, Broadbent JC, et al: St Marys Hospital-Mayo Clinic medical intensive-care unit—II. Patient population. Mayo Clin Proc 1967 Jun; 42:332-338

7. Cullen DJ, Ferrara LC, Briggs BA, et al: Survival, hospitalization charges and follow-up results in critically ill patients. N Engl J Med 1976 Apr 29; 294:982-987

8. Griner PF: Treatment of acute pulmonary edema: Conventional or intensive care? Ann Intern Med 1972 Oct; 77:501-506

9. Thibault GE, Mulley AG, Barnett GO, et al: Medical intensive care: Indications, interventions, and outcomes. N Engl J Med 1980 Apr 24; 302:938-942

10. American Hospital Association: Hospital Statistics, 1978 ed. Chicago, American Hospital Association, 1978

11. Turnbull AD, Carlon G, Baron R, et al: The inverse relationship between cost and survival in the critically ill cancer patient. Crit Care Med 1979 Jan; 7:20-23

12. Civetta JM: The inverse relationship between cost and survival. J Surg Res 1973 Mar; 14:265-269

WMS Annual Meeting & Scientific Program Schedule

June 30-July 3, 1982 • Jackson Lake Lodge • Moran, Wyoming

PROGRAM

WEDNESDAY, JUNE 30

8:00 am
WMS HOUSE OF DELEGATES OPENING SESSION

9:30 am to 12:30 pm
JOSEPH V. LEVY, PhD
An Update on Cardiovascular Drugs Including Focus on Hypertension, Ischemic Heart Disease, Antiplatelets and more

2:00 pm to 4:30 pm
WMS REFERENCE COMMITTEE MEETINGS

THURSDAY, JULY 1

8:00 am to 9:15 am
ROBERT S. ELIOT, MD
The Role of Life-style, Behavior and Stress in Cardiovascular Disease

9:30 am to 10:45 am
ROBERT S. ELIOT, MD
Practical and Clinical Measurements of Stress

11:00 am to 12:00 noon
ROBERT S. ELIOT, MD
Stress Management

1:30 pm to 4:30 pm (elective)
D. ROBERT HOWARD, MD; ARNOLD N. KRAUSE, MD and MORRIS B. MELLION, MD
Workshop—Coping with Stress and Professional Pressures

FRIDAY, JULY 2

8:00 am to 10:30 am
HELEN E. McILVAIN, PhD
Managing the Stressed Patient in the Medical and Surgical Setting

10:45 am to 12:00 noon
ROBERT E. HALES, MD
The Assessment, Prevention and Management of Physician Burnout

SATURDAY, JULY 3

8:30 am to 10:30 am
WMS HOUSE OF DELEGATES CLOSING SESSION

FACULTY

ROBERT S. ELIOT, MD
Professor of Medicine
Chairman, Department of Preventive and Stress Medicine
Director, Cardiovascular Center, University of Nebraska Medical Center

ROBERT E. HALES, MD
US Army, Division Surgeon
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WYOMING Medical Society

FOR PROGRAM, RESERVATIONS AND INFORMATION CONTACT:

WYOMING MEDICAL SOCIETY
Post Office Drawer 4009
Cheyenne, WY 82003-4009
Telephone (307) 635-2424

in memoriam

California Medical Association

EMGE, LUDWIG A., San Francisco. Died February 2, 1982, in Grass Valley, aged 96. Graduate of Rush Medical College, Chicago, 1915. Licensed in California in 1916. Dr. Emge was a retired member of the San Francisco Medical Society.

IANNE, CHARLES L., San Jose. Died December 20, 1981, in San Jose, aged 85. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1921. Licensed in California in 1921. Dr. Ianne was a retired member of the Santa Clara County Medical Society.

LOCARNINI, CHARLES ROBERT, Sonoma. Died January 25, 1982, in Santa Rosa of complications following enarterectomy, aged 57. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1950. Licensed in California in 1950. Dr. Locarnini was a member of the Sonoma County Medical Association.

STRONG, EDWARD K., San Francisco. Died February 1, 1982, aged 67. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1941. Licensed in California in 1941. Dr. Strong was a retired member of the San Francisco Medical Society.

TAYLOR, EMMETT C., San Francisco. Died December 28, 1981, aged 86. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Dr. Taylor was a retired member of the San Francisco Medical Society.

Utah State Medical Association

ANDERSON, WESLEY H., Ogden. Died February 14, 1982, in Ogden, aged 74. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1935. Licensed in Utah in 1936. Dr. Anderson was a member of the Weber County Medical Society.

GLASGOW, LOWELL ALAN, Salt Lake City. Died February 4, 1982, in Salt Lake City, aged 49. Graduate of the University of Rochester School of Medicine and Dentistry, Rochester, NY, 1958. Licensed in Utah in 1970. Dr. Glasgow was a member of the Salt Lake County Medical Society.

GUDMUNDSON, ARTHUR DANIEL, Ogden. Died February 4, 1982, in Ogden, aged 66. Graduate of the University of Louisville School of Medicine, 1943. Licensed in Utah in 1945. Dr. Gudmundson was a member of the Weber County Medical Society.

MAGID, STANLEY LEW, Salt Lake City. Died March 14, 1982, in Salt Lake City, aged 47. Graduate of the University of Nebraska College of Medicine, Omaha, 1960. Licensed in Utah in 1962. Dr. Magid was a member of the Salt Lake County Medical Society.

WOODRUFF, CHARLES W., Salt Lake City. Died February 12, 1982, in Salt Lake City, aged 85. Graduate of Northwestern University Medical School, Chicago, 1923. Licensed in Utah in 1923. Dr. Woodruff was a member of the Salt Lake County Medical Society.

Washington State Medical Association

CARLSON, INGE V., Bellevue. Died February 25, 1982, in Bellevue, aged 36. Graduate of Köbenhavns Universitet Laegevidenskabelige Fakultet, Köbenhavn, Denmark, 1973. Licensed in Washington in 1980. Dr. Carlson was a member of the King County Medical Society.

CONE, CARL B., Vancouver, WA. Died November 4, 1981, aged 77. Graduate of the University of Nebraska College of Medicine, Omaha, 1933. Licensed in Washington in 1935. Dr. Cone was a retired member of the Clark County Medical Society.

MCKINLEY, WILLIAM H., Silverdale. Died February 7, 1982, in Silverdale of brain tumor, aged 60. Graduate of the St. Louis University School of Medicine, St. Louis, 1954. Licensed in Washington in 1957. Dr. McKinley was a retired member of the Kitsap County Medical Society.

MORROW, CECIL L., Bellevue. Died January 20, 1982, aged 86. Graduate of Rush Medical College, Chicago, 1926. Licensed in Washington in 1927. Dr. Morrow was a retired member of the King County Medical Society.

PATRICELLI, LIBERINO C., Seattle. Died February 13, 1982, in Seattle, aged 74. Graduate of Harvard Medical School, Boston, 1936. Licensed in Washington in 1938. Dr. Patricelli was a retired member of the King County Medical Society.

STANDARD, JAMES F., Sequim. Died November 30, 1981, in Sequim, aged 71. Graduate of the Washington University School of Medicine, St. Louis, 1936. Licensed in Washington in 1937. Dr. Standard was a retired member of the Clallam County Medical Society.

WICKLUND, JEAN D., Seattle. Died January 23, 1982, in Seattle, aged 42. Graduate of the University of Washington School of Medicine, Seattle, 1965. Licensed in Washington in 1971. Dr. Wicklund was a member of the King County Medical Society.

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Recommend

NEOSPORIN® Ointment (POLYMYXIN B-BACITRACIN-NEOMYCIN)

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- Handy applicator tip

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NTRAINDICATIONS: Not for use in the eyes or in the external ear canal he eardrum is perforated. This product is contraindicated in those individuals) have shown hypersensitivity to any of its components.

RNING: Because of the potential hazard of nephrotoxicity and ototoxicity due eomycin, care should be exercised when using this product in treating extensive ns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section)

Complete literature available on request from Professional Services Dept. PML.

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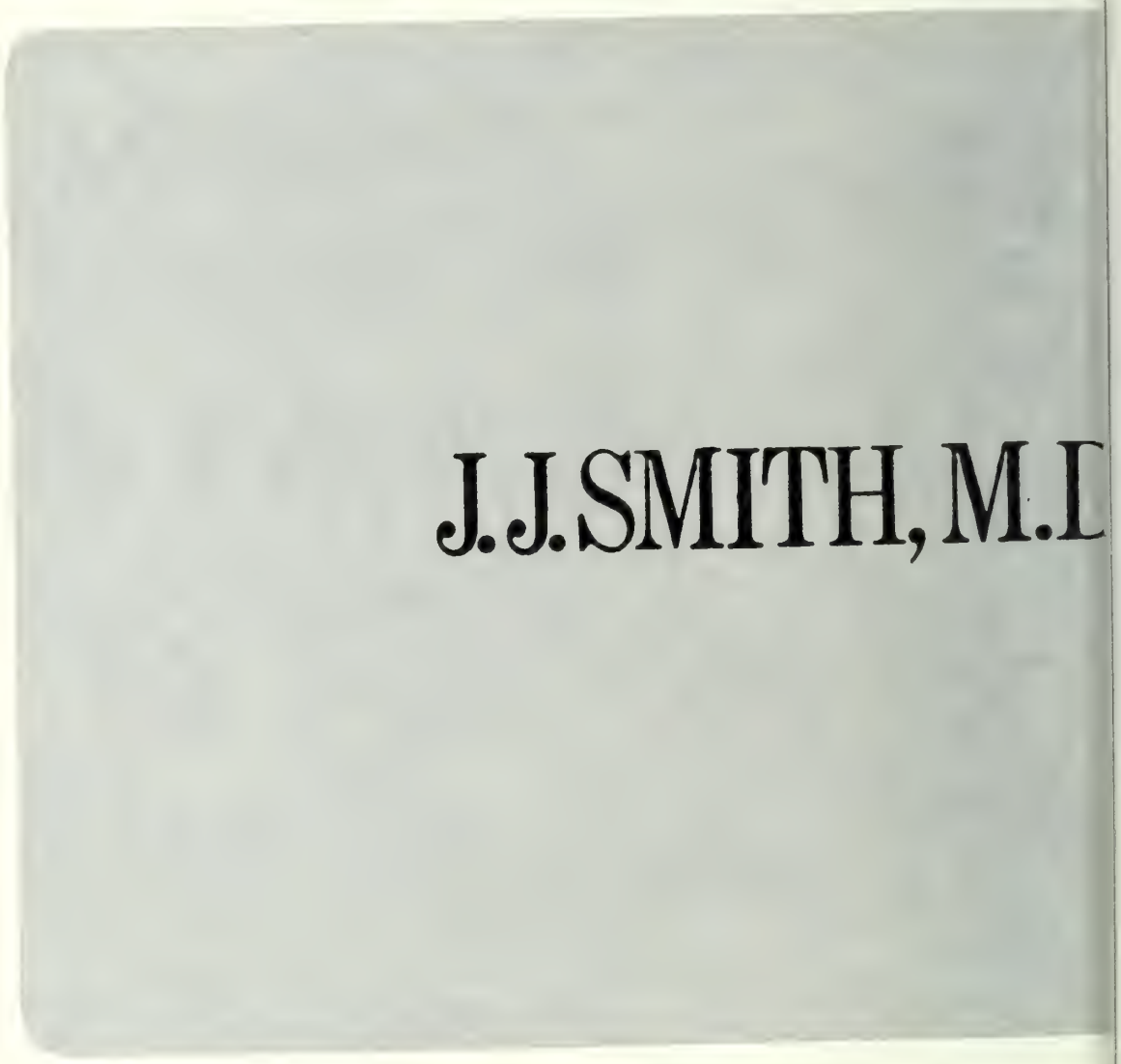

*For moderate to severe vasomotor symptoms, atrophic vaginitis, surgical menopause, postmenopausal osteoporosis†

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

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ated Estrogens Tablets have been evaluated as probably effective for postmenopausal
ptoms.
s no evidence that estrogens are effective for nervous symptoms or depression without
ated vasomotor symptoms.

e see following page for Brief Summary of Prescribing Information.

PHYSICIANS WHO CARE.

for atrophic vaginitis

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM

Premarin

0.625 mg/gm

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.
Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN-Tablets by the National Academy of Sciences - National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma – palliative therapy of advanced disease.
9. Postpartum breast engorgement. Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.
PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.
Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day, comparable to those used to treat cancer of the prostate and breast) have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. While doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.
Benign hepatic adenomas should be considered in estrogen users having abdominal pain or tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.
PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormally excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen therapy. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, and in young patients in whom bone growth is not complete.
The following changes may be expected with larger doses of estrogen:
a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3, increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.
As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.
ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis; change in cervical erosion and in degree of cervical secretion; cystitis like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache; migraine; dizziness; mental depression; chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.
ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.
DOSAGE AND ADMINISTRATION:
PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Administration should be cyclic (*e.g.*, three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
2. *Given cyclically.* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.
Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.
If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.
Female castration and primary ovarian failure. 1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.
Osteoporosis (to retard progression). 1.25 mg daily, cyclically.
3. *Given for a few days.* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.
4. *Given chronically.* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.
Inoperable progressing breast cancer in appropriately selected men and postmenopausal women. 10 mg three times daily for a period of at least three months.
Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurrent abnormal vaginal bleeding.
PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream
Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Administration should be cyclic (*e.g.*, three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.
Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.
HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865 - Each *pink* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866 - Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867 - Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868 – Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.
PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream – No. 872. Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)
Combination package. Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.
Also Available. Refill package. Each contains Net Wt. 1½ oz. (42.5 g) tube. 7814

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(Continued on Page 54)

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Opportunities are available for internists, family practitioners and psychiatrists to work with developmentally disabled people in State residential communities. Locations from Los Angeles to northern California. Challenging and varied cases, congenial professional environment, excellent civil service benefits.

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RIMSO®-50
(dimethyl sulfoxide)
50% w/w aqueous solution

INDICATIONS AND USAGE

RIMSO® - 50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. RIMSO ® - 50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.

CONTRAINDICATIONS

None known.

WARNINGS

Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical RIMSO® - 50. The physican should be cognizant of this possibility in prescribing RIMSO® - 50. If anaphylactoid symptoms develop, appropriate therapy should be instituted.

PRECAUTIONS

Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of RIMSO® - 50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation.

Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO® - 50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide.

The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.

DOSAGE AND ADMINISTRATION

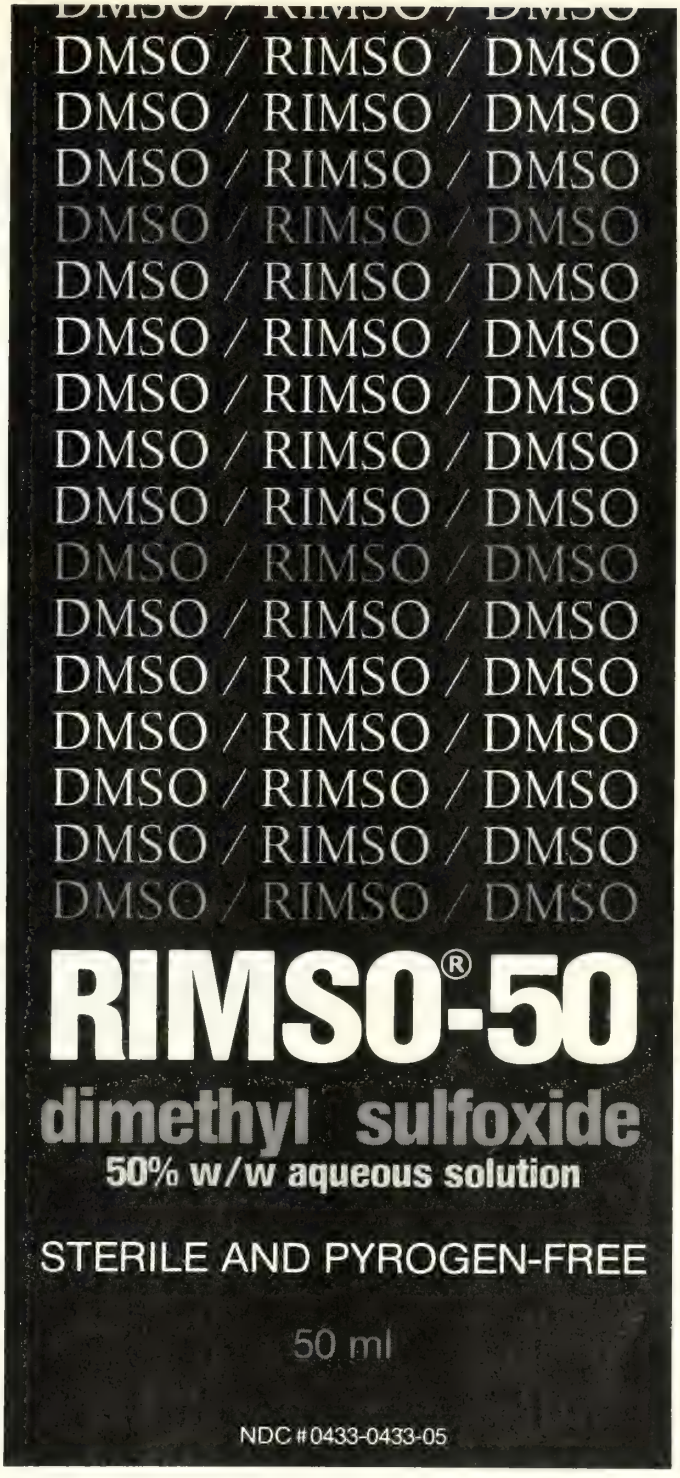
Instillation of 50 ml of RIMSO® - 50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as lidocaine jelly to the uretha is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately.

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO® - 50 can reduce bladder spasm.

In patients with severe interstital cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia. (Saddle block has been suggested)

HOW SUPPLIED

Bottles contain 50 ml of sterile and pyrogen-free RIMSO® - 50 (50% w/w dimethyl sulfoxide aqueous solution).
Dimethyl sulfoxide is clear and colorless.
Protect from strong light.
Store at room temperature (50° to 86°F) (15° to 30°C).
Do not autoclave.
NDC # 0433-0433-05



FOR FURTHER INFORMATION

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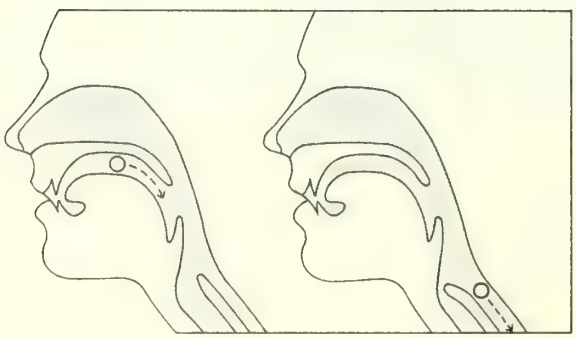
If you've never recommended a specific brand of aspirin before, now's the time to start!

Better tolerated than regular aspirin



Now, by means of a unique water-soluble cellulose coating, Improved Bayer® Aspirin provides oro-pharyngo-esophageal protection for your patients. Furthermore, in a recent short term use study, perceived stomach upset was shown to be no greater than seen with placebo.[1]

This patented coating is *not* enteric in nature so it is not affected by pH. And the film does not affect absorption or bioavailability. What it does is to stay intact just long enough for tablets to reach the stomach. Disintegration in the buccal cavity, pharynx and esophagus is avoided—easing swallowing and minimizing aspirin

aste, aftertaste and burning in the throat. Once ablets reach the stomach, they dissolve uickly and completely—producing the same spirin and salicylate blood levels as regular spirin.[2]

rotective effect demonstrated n multi-center study[1]

a double-blind, multi-center clinical study,[1] ivolving 907 subjects, Improved Bayer Aspirin as shown significantly superior to regular spirin in avoiding aspirin taste, aftertaste, dis-olution of tablets in the mouth and burning in he throat.

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What's more, for hort term use when ompared to both oated and un-oated placebo tab-ts, Improved Bayer spirin showed *no gnificant differ-ence in subjective omplaints of stom-ch upset*-as shown in the chart:

Subjective evaluations—average percentage of complaints following each of three 650 mg doses of Improved Bayer Aspirin, placebo and coated placebo—given four hours apart[1]

Symptom & Time of Administration*	Improved Bayer Aspirin	Placebo	Coated Placebo
Burning in Throat			
5 min.	6%	5%	5%
20 min.	8%	7%	8%
50 min.	6%	5%	5%
Stomach Upset			
5 min.	2%	4%	2%
20 min.	6%	8%	5%
50 min.	8%	7%	5%
Nausea			
5 min.	0%	1%	0%
20 min.	2%	3%	2%
50 min.	3%	2%	2%

* Following each of the three doses of test formulations, subjective side effects were recorded at 5, 20 and 50 minutes.

Better patient compliance

With its low incidence of subjective complaints and high degree of acceptance, Improved Bayer Aspirin can help assure the kind of patient compliance needed for successful salicylate therapy.

Now, more than ever—Bayer is the name to specify

To be sure your patients get all the benefits of Improved Bayer Aspirin, be sure to specify the name Bayer, whenever you recommend aspirin. Now, more than ever, it can make an important difference.

References:
1. Soller, R. W. and Baretz, D.B.: Methylcellulose Film Coating of Tablets as an Improved Delivery System for Aspirin (to be published).
2. Soller, R. W.: Bioavailability of Improved Bayer Aspirin (on file, The Bayer Company).

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SPOT-RESISTANT ORAL CONTRACEPTION IS HERE!

It's LO/OVRAL 30. And here's how it holds spotting and breakthrough bleeding to a minimum: Hormone balance right from the start...and throughout the cycle. Hormone balance made possible with a very low dose oral contraceptive because of the supportive progestational activity of norgestrel, Wyeth's exclusive progestogen.

Regular withdrawal bleeding, too despite its low dose. In clinical trials amenorrhea—defined as absence of bleeding in the 7 pill-free days—was reported in only 2.1% of total cycles. And when defined as absence of bleeding for 60 days or more (as it often is), the incidence was only 0.2%.*

And comfort for most patients* thanks to the same balance that helps prevent spotting and breakthrough bleeding. In the clinical trials, most patients stayed free of common side effects such as nausea (0.6% of cycles), vomiting (0.1%), depression (0.5%) and acne (0.9%).

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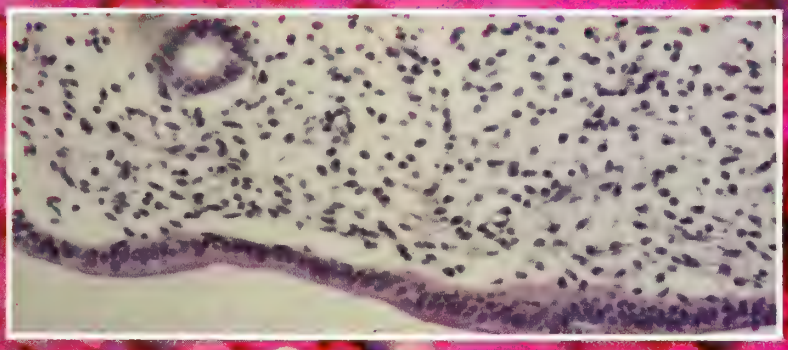
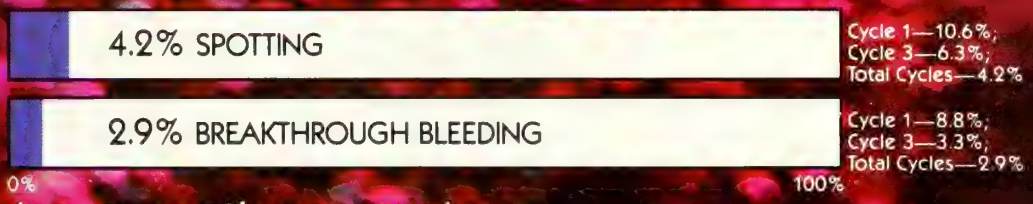


LO/OVRAL—1st cycle
Biopsy of intact endometrium in stable, progestogen suppressed state. Small, tubular gland in loose stroma without hemorrhage, fragmentation or debris characteristic of desquamating endometrium.

Even in the first cycle, the effective action of LO/OVRAL on the endometrium, such as you see here, provides the resistance against spotting and breakthrough bleeding you hope to achieve.

HISTOLOGICALLY... AND CLINICALLY.



A near-spotless record— in clinical trials involving 22,489 cycles*

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. Contraindications, Warnings, Precautions, Adverse Reactions, etc., in the accompanying In Brief should be carefully considered.

See full prescribing information.

LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth

...with a near-spotless record!

See important information on following page.

IN BRIEF:

Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3. Cerebral-vascular or coronary-artery disease
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000, ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately

A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's, effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema, chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic), mental depression; reduced tolerance to carbohydrates, vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

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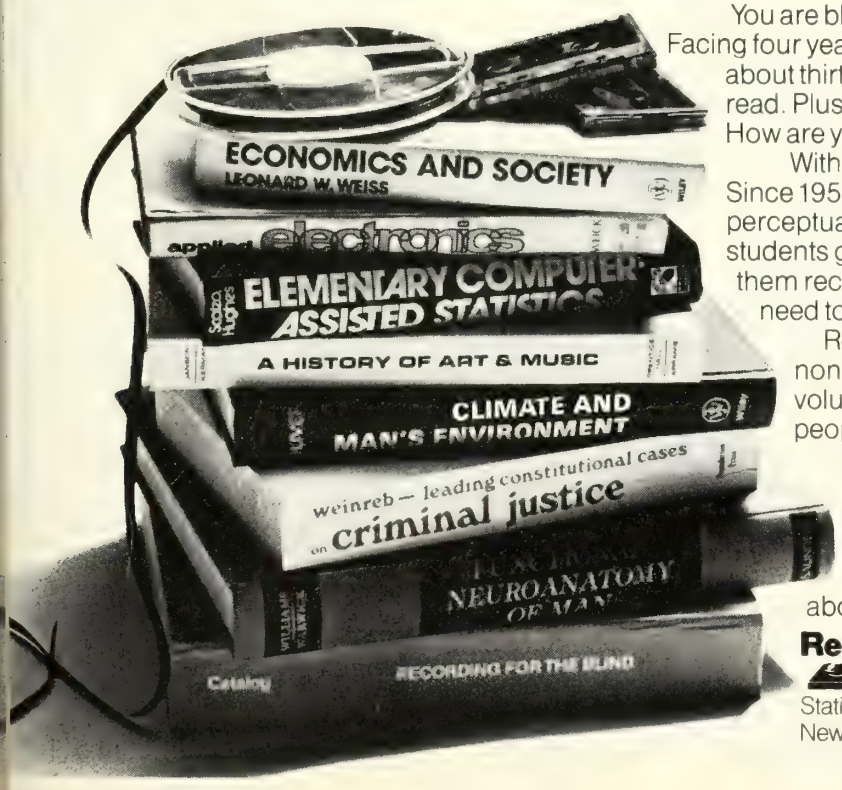

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(Continued from Page 46)

PHYSICIANS WANTED

OPPORTUNITY FOR HEMATOLOGY-ONCOLOGY FELLOWSHIP. Applications are being accepted for anyone interested in an exciting fellowship program at Fitzsimons Army Medical Center, Aurora, Colorado to start in July 1983. Fitzsimons is located in the Denver metropolitan area with access to skiing and other recreational activities available in the Colorado Rockies. This fellowship program is open to U.S. citizens who are board certified in Internal Medicine. Heavy emphasis is placed on patient care, clinical experience as well as research in both Hematology and Medical Oncology, including coagulation, and cooperative group protocols. Fellows who are accepted to the program are required to serve on active duty as commissioned officers in the U.S. Army during training, and for 2 years following completion. Annual salary is approximately $35,000-$40,000 depending upon prior military service and background. In addition, fellows are entitled to full benefits as a commissioned military officer during training and following. For further information, please call (303) 361-8001 or 361-8307 or write COL Nicholas J. DiBella, MD, Chief, Hematology-Oncology Service, Fitzsimons Army Medical Center, Aurora, CO 80045.

WANTED: Internist conversant in GP, midwest community of 6,000. Annual compensation approximately $84,000. Write or phone: Lynch Clinic, PC, 620 5th, Fairbury, NE 68352. (402) 729-2281.

TWO FULL-TIME PHYSICIAN VACANCIES for general medical care in the Student Health Service, The Claremont Colleges, 20 miles east of Los Angeles. Prefer family practice, adolescent medicine or internal medicine background. $42,000 minimum salary, plus fringe benefits. Submit résumé by May 15, 1982 to: Medical Search Committee, Personnel Services, The Claremont Colleges, 747 No. Dartmouth Ave., Claremont, CA 91711. EEO/AA Employer.

FREESTANDING EMERGENCY CLINIC seeks a competant, people oriented physician for a stable position with remarkable growth potential. The setting is an attractive area 3 hours from San Francisco. Please reply to box 6294, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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SENIOR RESEARCH ASSOCIATE—Salary $34,000-$40,000, must have a PhD degree and substantial research experience in two or more of following fields: biochemistry of membranes and receptors, humoral and cellular immunology, tissue culture and hybridoma techniques, radioimmunoassay, tumor biology and endocrinology. Responsible for managing research laboratory, supervision of research projects, supervision of laboratory personnel, including postdoctoral fellows, research assistants and students. Participate in seminars and other teaching activities. Prior experience in writing manuscripts for various publications and successful grant/contract applications. Employer is an equal opportunity employer. Applicants should apply to Mr. James Peters, California Employment Development Department, 297 West Hedding, San Jose, California 95110 by June 10, 1982.

AN ACADEMICAN, family physician, scholar and research leader is sought for a tenure tract position at either Assistant or Associate Professor level. Applicants should have several publications and a successful record of accomplishment in research related to Family Medicine. Some clinical teaching and routine faculty duties are required but the primary thrust of this position will be to serve as an investigator and catalyst for others in the department. Please send CV to J. Dennis Mull, MD, Dept. of Family Medicine, UCI Medical Center, 101 City Dr. So., Orange, CA 92668 by May 15, 1982. An Affirmative Action/Equal Opportunity Employer.

ACTIVE OHIO PARTNERSHIP OFFERS ONE YEAR FELLOWSHIP in Intraocular Lens Implantation, Posterior Chamber, Anterior Chamber, Intracapsular, Extracapsular, Phacoemulsification. Forty-thousand plus fringes. Send CV and career objectives to P.O. Box 6293, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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OPHTHALMOLOGIST: Over 45, Wanted with interest in Medical Ophth, Peds/Strabismus, Plastics/Orbit or Neuro-Ophth. Dennis Shepard, MD, 1414 E. Main St., Santa Maria, CA 93454. (805) 925-2637.

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ACTIVE RURAL HEALTH CENTER in Central California near Sierras has temporary pharmacist position F/T (4-6 months) w/possibility for permanent employment. Responsibilities include purchasing and distributive services for outpatient family practice w/multiple providers. 1 year experience required. Clinical training and ability to speak Spanish appreciated. Contact: M. Stassinos, PharmD, Ten Community Health Center, P.O. Box H, Earlimart, CA 93219. (805) 849-2638.

FAMILY NURSE PRACTITIONER

MN, WITH National Certification and Prescriptive Authority desires Family Practice or ER position. Three years experience in rural family practice, ACLS qualified, trauma experience and strong clinical background. Very versatile. Please reply Box 6295, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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PRACTICES AVAILABLE

TO SELL OR BUY A MEDICAL PRACTICE, or to arrange an association, contact Physicians Clearinghouse, Mary Bradshaw, 21 Altamount Dr., Orinda, CA 94563. (415) 376-0762. Consulting, Appraising, Partnerships, Placement.

PRACTICE AND EQUIPMENT. Ophthalmologist retiring, will sell practice and/or equipment for cost of equipment only. Anaheim, California location for the past 20 years. Phone or write for further information to: Joseph S. Holowin, MD, 710 S. Brookhurst Suite A, Anaheim, CA 92804. (714) 772-5740.

PARTNERSHIP WANTED

FAMILY PRACTICE—We are two PAs, one Internist looking for one FP. Rural South Central Washington. But close to everything out of doors. Salary to start then partnership. Grandview Family Practice Clinic, 242 Division, Grandview, WA 98930.

ASSOCIATE WANTED

PART-TIME RADIOLOGIST to do general radiology in office. Excellent retirement situation. Beautiful area of Northwest. Box 6298, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SITUATIONS WANTED

ORTHOPEDIC SURGEON BOARD CERTIFIED, University trained Member of American Academy of Orthopedic Surgeons. Wants office Orthopedics, evaluations etc. Part or full time. Please write to Box 6299, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

60 YEAR OLD IRISHMAN. Dublin graduate. Working in the Geriatric Dept. of a State Psychiatric Hospital on the East Coast for the past 15 years. Fellow of The American Geriatric Society since 1962. Licensed to practice in California. Would like to work for a convalescent home chain catering for title 19 patients etc. Would be prepared to invest money in an expansion program. Income expected about $60,000 to $75,000 a year for 35 hour week. Please outline your proposal. Box 6296, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CALIFORNIA TRAINED INTERNIST—Anxious to return to the Southern West Coast. Currently assistant professor at top midwest university. Box 6297, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PEDIATRICIAN—32, completing pulmonary-neonatal fellowship with strong interest in developing pediatric intensive care services seeks full time position. BE Pediatrics & Neonatalogy. Box 6289, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OB/GYN—Age 45 with 12 years experience of OB/GYN outside U.S. Presently resident in OB/GYN in University of California Irvine Medical Center, interested to share a practice, associate or employed in Southern California or other western or midwest states (license in California) from July 1982. Reply Box 6300, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

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Army Medical Department Opportunities

The Army Medical Corps offers virtually unlimited opportunities to learn, teach, investigate, practice and direct. For physicians who want more in their health care career than a predictable daily routine, the Army Medical Corps has a lot to offer. There are challenging professional opportunities in patient care, preventive medicine, research, administration and education. A variety of excellent educational programs exist. As a member of the Army Medical Corps, you become a part of one of the largest comprehensive systems of health care in the United States. Numerous medical facilities exist in most states, ranging from clinics and hospitals to world-reknowned medical centers. For more information...

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San Francisco, CA (415) 561-3126
Los Angeles, CA (714) 836-2355

(Continued from Page 37)

Friday-Saturday. 12 hrs. Contact: Leanne Stone, Cont. Ed., Univ. of Nevada-Reno, Reno 89557. (702) 784-4046.

August 14-25—**25th Annual Postgraduate Refresher Course.** USC at Sheraton Waikiki, Honolulu, and Maui Marriott Resort, Maui. 12 days. 37 hrs. $425.

August 16-20—**Advanced Diving Medicine.** UCSF at San Diego. Monday-Friday.

August 23-September 3—**Intensive Residency in Occupational Medicine, Session. I.** UCSF at Golden Gateway Holiday Inn, San Francisco. 12 days. 80 hrs. $1,000.

August 27-29—**Physicians—Stress and Coping.** CMA at La Playa Hotel, Carmel. Thursday-Sunday. 14 hrs. $190 per couple or $120 per person. Contact: Sandy Willett, CMA.

August 29-September 3—**Family Practice Refresher Course.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday.

September 10-12—**Physicians—Stress and Coping.** CMA at Sea Lodge, La Jolla. Thursday-Sunday. 14 hrs. $190 per couple or $120 per person. Contact: Sandy Willett, CMA.

September 16-18—**Postgraduate Institute on Geriatrics.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

September 20-22—**Alcoholism Treatment—Cooperation or Competition.** Alcoholism Treatment Center of Scripps Memorial Hosital at Vacation Village, San Diego. Monday-Wednesday. $190. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

October 4-7—**American Academy of Family Physicians—1982 Scientific Assembly.** Moscone Center, San Francisco. Monday-Thursday. 30+ hrs. $50, members; $75, nonmembers. Contact: Edward E. Daleske, Committee on Scientific Prog., AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

October 8-10—**Physicians—Stress and Coping.** CMA at Half Moon Bay Lodge, Half Moon Bay. Thursday-Sunday. 14 hrs. $190 per couple or $120 per person. Contact: Sandy Willett, CMA.

October 9-10—**Update on Bone and Calcium.** UCSF. Saturday-Sunday.

October 10-15—**American Physiological Society—33rd Annual Fall Meeting.** Town and Country, San Diego. Sunday-Friday. Contact: Geri Goodenough, Scientific Meetings, APS, 9650 Rockville Pike, Bethesda, MD 20814. (301) 530-7010.

October 11-14—**Hawaii Medical Association—126th Annual Scientific Meeting.** Hilton Hawaiian Village, Honolulu. Monday-Thursday. Contact: Irene Wong, HMA, 320 Ward Ave., Honolulu 96814. (808) 536-7702.

October 28-30—**West Coast Counties Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

November 1-4—**Interstate Postgraduate Medical Association—67th Scientific Assembly.** Town and Country, San Diego. Monday-Thursday. 24 hrs. Contact: H. B. Maroney, Exec. Dir., P.O. Box 1109, Madison, WI 53701. (608) 257-6781.

November 1-5—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $365.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA

See Washington Listings: May 26; June 7, 8, 17-18.

IDAHO

July 28-31—**Idaho Medical Association 90th Annual Meeting.** Sun Valley. For information contact IMA, P.O. Box 2668, Boise, ID 83761. (208) 344-7888.

See also Washington Listings: May 29 and June 14.

MONTANA

September 9-11—**Adult and Pediatric Chest Diseases—Current Views 1982.** Bigfork. Thursday-Saturday. Flathead Lake Lodge. Contact: American Lung Association of Montana, 828 Helena Ave, Helena, MT 59601. (406) 442-6556.

October 30-November 2—**Montana Medical Association Annual Meeting.** Great Falls. Friday-Tuesday. Sheraton. For information contact: Montana Medical Association, 2011 Eleventh Avenue, Suite 12, Helena, MT 59601. (406) 443-4000.

See also Washington Listings: May 26, 27, 28; June 7 and 8. 28; June 7 and 8.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

(Continued on Page 58)

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213-795-0432

(Continued from Page 56)

May 14-15—**15th Annual OB/GYN Update.** Albuquerque. Friday-Saturday. AMFAC Hotel. 10 credit hours, also AAFP Prescribed. Contact: UNM School of Medicine, Office of CME, Albuquerque, NM 87131. (505) 277-3942.

June 4-5—**Recent Advances in the Diagnosis and Treatment of Coronary Artery Disease.** Albuquerque. Friday-Saturday. Veterans Administration Medical Center. 10 credit hours, also AAFP Prescribed. Contact: American Heart Association, 2403 San Mateo Blvd., Albuquerque, NM 87108. (505) 884-3717.

June 10-11—**Advanced Trauma Life Support Provider's Course.** Albuquerque. Thursday-Friday. Burn & Trauma Unit, UNM Hospital. 16 credit hours. Contact: William Schiller, MD, UNM Hospital, Albuquerque, NM 87131. (505) 843-2270.

June 17-19—**Radiology for Primary Care Physicians 1982—An Update.** Santa Fe. Thursday-Saturday. Symposia de Santa Fe. 15 credit hours, also AAFP Prescribed. Contact: Marcus J. Smith, MD, PO Box 5175, Santa Fe, NM 87501. (505) 982-5218.

July 8-10—**25th Annual Meeting, New Mexico Ophthalmological Society.** Santa Fe. Thursday-Saturday. Hilton Inn. 8 credit hours. Contact: Walter J. Levy, MD, 465 St. Michael's Dr., Santa Fe, NM 87501. (505) 982-1911.

July 19-22—**25th Annual Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 credit hours. Also AAFP Prescribed. Contact: Convention Director, NM Academy of Family Physicians, PO Box 456, Sunland Park, NM 88063. (505) 266-7868 or (915) 533-3449.

July 23-25—**11th Annual Santa Fe Cardiology Symposium.** Santa Fe. Friday-Sunday. Inn at Loretto. 14 credit hours, also AAFP Prescribed. Contact: Meeting Director, Southwest Cardiology Associates, 8100 Constitution NE, Albuquerque, NM 87110. (505) 292-1114.

July 29-31—**General Surgical Update—82.** Albuquerque. Thursday-Saturday. Classic Hotel. 15 credit hours, also AAFP Prescribed. Contact: UNM School of Medicine, Office of CME, Albuquerque, NM 87131. (505) 277-3942.

October 7-9—**The Clinical Spectrum of Adult Heart Disease.** Albuquerque. Thursday-Saturday. University of New Mexico School of Medicine Auditorium. Hour for hour credit, also AAFP Prescribed. Contact: Jonathan Abrams, MD, UNM, School of Medicine, Dept. of Cardiology, Albuquerque, NM 87131. (505) 277-4253.

January 15-16—**Semi-Annual Clinical Meeting: New Mexico Academy of Family Physicians.** Albuquerque. Saturday-Sunday. Marriott Hotel. 12 credit hours, also AAFP Prescribed. Contact: New Mexico Academy of Family Physicians, 303 San Mateo NE, #204, Albuquerque, NM 87108. (505) 266-7868.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene. OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

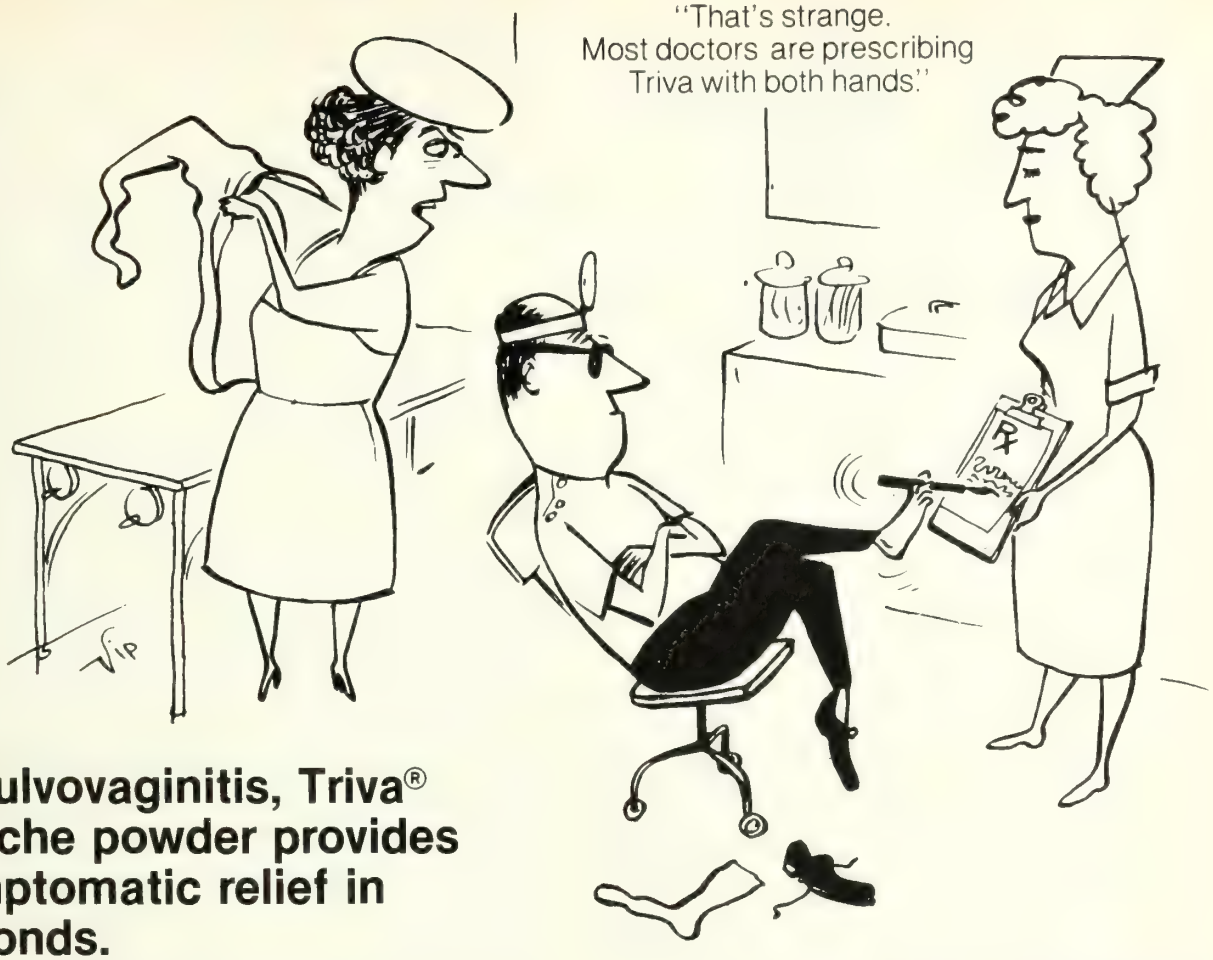
FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD,

(Continued on Page 61)

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.



In vulvovaginitis, Triva® douche powder provides symptomatic relief in seconds.

Relief in seconds. That's how quickly Triva goes to work to help your vaginitis patients. And that's just after their first douche. Within 12 days of recommended treatment with Triva, most cases of trichomonal and non-specific vaginitis are organism-free. (Monilial infection may take a bit longer.) Also, your patients can start therapy right away, because with Triva there's no need to worry about contraindications associated with causative organisms.

Triva® Douche Powder

Oxyquinoline Sulfate 2.0%, Alkyl Aryl Sulfonate 35.0%, Sodium Sulfate 62.5%, Disodium EDTA .33%.

Combines flushing douche action with the chemical action of its formula. For treatment of Trichomonas infestation, Triva Douche Powder may be used adjunctively with oral therapy for fast symptomatic relief.

Rx Triva® Jel

Per 5 grams: oxyquinoline benzoate 7.5 mg.; alkyl aryl sulfonate 62.5 mg.; disodium edetate 2.5 mg.; aminacrine HCl 10 mg.; copper sulfate .063 mg.; sodium sulfate 6.9 mg.

Provides the effective therapeutic action of Triva with the continuous action of the jel form, to quickly arrest infection and aid in relief of symptoms.

Rx Triva® Combination

Combines therapeutic Douche Powder and Triva Jel with a handy applicator in a convenient, complete treatment kit. Triva Combination effectively treats all three types of vaginitis, including stubborn cases where Monilia and Trichomonas occur together. Effectiveness of Triva Combination has been demonstrated by clinical testing involving the use of Papanicolaou smear and Sabouraud culture to confirm diagnosis and cure.

Precaution
If irritation occurs at the onset of treatment with Jel, treatment may be postponed for a day or two and preliminary treatment with ½ strength Triva Douche used. Regular treatment should then be resumed.

Other Ethically Promoted Products from Boyle & Company:

- Citra Capsules . . . Antihistaminic/Decongestant/Analgesic for cold symptoms relief
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- Glytinic Tablets and Liquid . . . Iron plus aminoacetic acid for iron deficiency anemia

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THE WESTERN JOURNAL OF MEDICINE
INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 731 Market Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed double-spaced throughout (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers, and month and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Andersen HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978 Apr 26; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978 Sep; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role piaying in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, IL, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, MA, Publishing Sciences Group, Inc, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

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Reprints

If reprints are desired, they must be paid for by the author. A reprint order form with schedule of prices is sent to the author when the article is published. Authors are responsible for handling requests for reprints of their articles.

(Continued from Page 58)

Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

OBSTETRICS AND GYNECOLOGY

October 21-23—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

SURGERY

June 4-5—**Orthopedics for the Primary Care Physician.** Portland. Friday-Saturday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

December 3—**Soft Tissue Surgery Techniques.** Portland. Friday. Oregon Health Sciences University Campus. For information contact: OHSU-CME.

INTEREST TO ALL PHYSICIANS

June 18—**Small Cell Carcinoma of the Lung.** Portland. Friday. Oregon Medical Association Building. For information contact: OHSU-CME.

June 24-25—**Urology for the Non-Urologist.** Portland. Thursday-Friday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

September 10-11—**Ashland Conference: Antimicrobial Therapy in Perspective: The Place of the New Drugs.** Ashland. Friday-Saturday. Ashland Hills Inn. For information contact: OHSU-CME.

October 29-31—**Salishan Conference: Cardiology.** Gleneden Beach. Friday-Saturday. Salishan Lodge. For information contact: OHSU-CME.

November 4-5—**Sommer Lectures—Oregon Medical Association Annual Meeting.** Portland. Thursday-Friday. Thunderbird Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

November 18-19—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

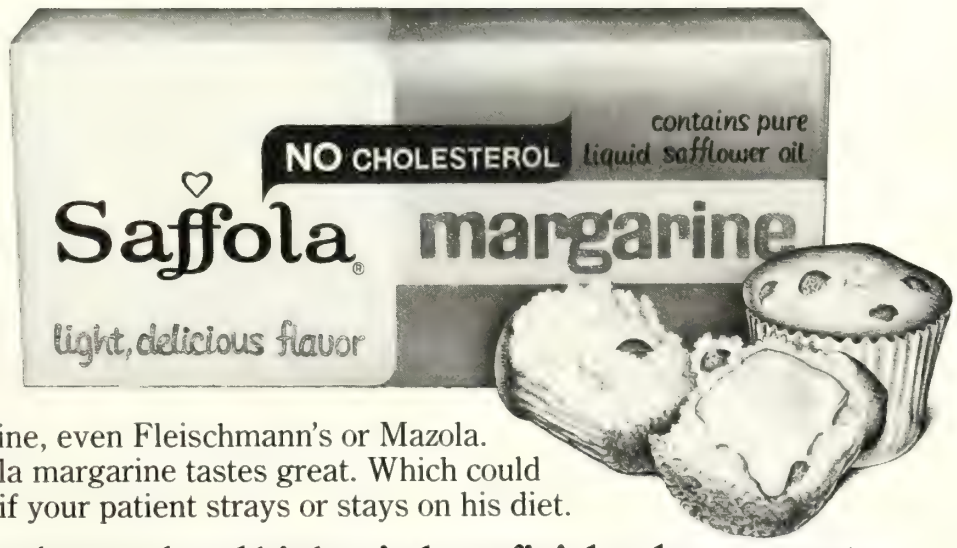
NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

(Continued on Page 63)

Cheer up a low cholesterol diet with Saffola.



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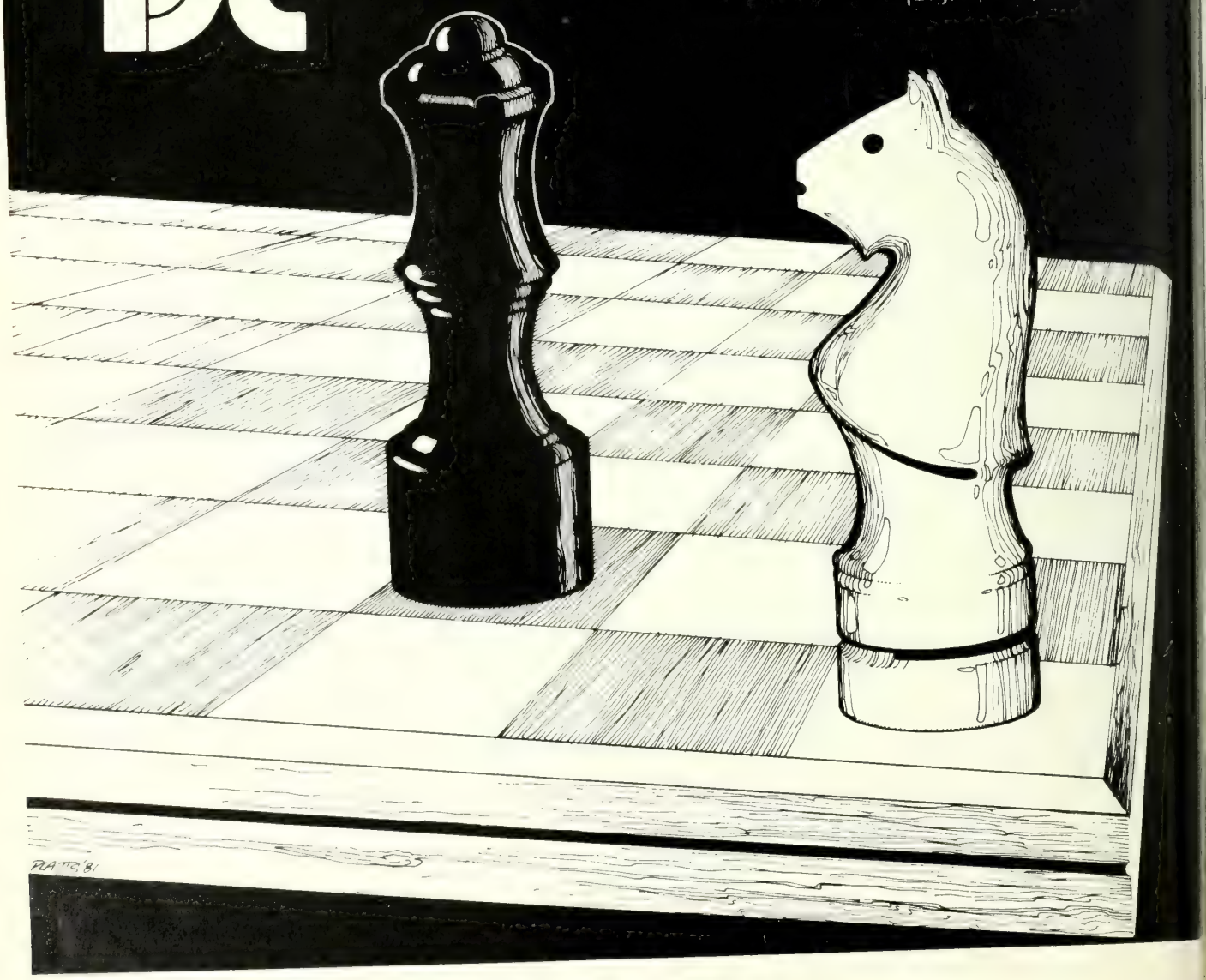

(Continued from Page 61)

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

MKSAP V REVIEW

(Sponsors: Utah Region, American College of Physicians/Utah Society of Internal Medicine/University of Utah)
University Medical Center, Salt Lake City

October 1981-June 1982 (Ongoing)—Thursdays. 2 hrs. Fee for Optional Materials: $160 (ACP non-members); $60 (ACP members). Contact: John Holbrook, MD (801) 581-7818.

* * * *

May 14-15—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

May 19-21—**The Ogden Surgical Society 37th Annual Meeting** (Sponsor: The Ogden Surgical Society). Ogden. Wednesday-Friday. Weber State College. 22 hrs. CME registration fee: $10. Contact: Phyllis McDonald (801) 825-5589.

June 2-5—**First Annual BYU Conference on Sports Medicine** (Sponsor: Utah Valley Hospital). Provo. Wednesday-Saturday. Brigham Young University Conference Center. 18 hrs. Fee: $295. Contact: Steve Mack (801) 378-4851.

(Continued on Page 66)

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

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Contact your local Arthritis Foundation chapter for the latest information on arthritis. This includes continuing educational seminars by leading rheumatologists, scientific meetings, "outreach" programs—as well as the "Bulletin on the Rheumatic Diseases," "Arthritis and Rheumatism Journal," "Primer on the Rheumatic Diseases," audio cassettes and other professional materials. Free disease handbooks and medication pamphlets are also available to patients.

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(Continued from Page 63)

June 10-11—**6th Annual Castle Country Medical Symposium and Rock Art Jeep Safari** (Sponsor: Castleview Hospital). Price. Thursday-Friday. Price Elks Lodge. 12 hrs. Fee: $100. Contact: Mary Louise Ghirardelli (801) 637-4800.

June 11-12—**Medical Aspects of Laser Surgery** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Little America. Credit and fee to be announced. Contact: John Dixon, MD (801) 581-8201.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

May 13-15—**Third Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 14—**Medical Alumni.** Seattle. Friday. U/W Hogness Auditorium. Contact: U/W.

May 14-15—**Therapeutics in Common Medical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 19—**Breast Cancer & Acute Leukemia.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

May 20—**Estrogen Controversy.** Tacoma. Thursday. Contact: CME Pierce County.

May 20-22—**3rd Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 21-22—**Transition Into Independence: The Physically Disabled Adolescent.** Seattle. Friday-Saturday. Children's Orthopedic Hospital and Medical Center, Wright Auditorium. Contact: Carly Gimble. (206) 634-5707.

May 24—**Fever Unknown Origin/Dx Elderly Dementia.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

May 26—**(ALASKA) Vaginitis.** Anchorage. Wednesday. Contact: U/W.

May 26—**(MONTANA) Health Problems of Physicians.** Great Falls. Wednesday. Deaconess Hospital. Contact: U/W.

May 26—**(MONTANA) Site Visit.** Kalispell. Wednesday. Contact: U/W.

May 27—**(MONTANA) Health Problems of Physicians.** Billings. Thursday. Marillac Hall. Contact: U/W.

May 27—**(MONTANA) Site Visit.** Whitefish. Thursday. Contact: U/W.

May 27-28—**Current Concepts in Management of Joint Disease.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

May 28—**(MONTANA) Health Problems of Physicians.** Missoula. Friday. St. Patrick Hospital. Contact: U/W.

May 28-29—**Advanced Cardiac Life Support.** Seattle. Thursday. U/W Health Sciences Building. Contact: U/W.

May 29—**(IDAHO) Site Visit.** Pocatello. Saturday. Contact: U/W.

June 3-5—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

June 7—**(MONTANA) Site Visit.** Kalispell. Monday. Contact: U/W.

June 7—**(ALASKA) Site Visit.** Ketchikan. Monday. Contact: U/W.

June 8—**(ALASKA) Site Visit.** Anchorage. Tuesday. Contact: U/W.

June 8—**(MONTANA) Site Visit.** Whitefish. Tuesday. Contact: U/W.

June 10-12—**Common Minor Surgeries.** Seattle. Thursday-Saturday. Park Hilton. Contact: U/W.

June 14—**(IDAHO) Vaginitis.** Boise. Monday. Contact: U/W.

June 14—**Site Visit.** Omak. Monday. Contact: U/W.

June 15—**Vaginitis.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

June 15—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

June 16—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

June 17-18—**(ALASKA) Behavior Medicine for GP's.** Anchorage. Thursday-Friday. Contact: U/W.

June 19-23—**(BRITISH COLUMBIA, CANADA) Canadian Congress of Laboratory Medicine & Pacific Northwest Society of Pathologists Meeting.** Vancouver, BC. Saturday-Wednesday. Hotel Vancouver. Contact: G. R. Gray, MD, 201-660 West Seventh Avenue, Vancouver, BC V5Z IB5.

June 21-25—**Internal Medicine Review.** Seattle. Monday-Friday. Park Hilton. Contact: U/W.

June 22—**Pearls in Office Practice—6th Annual Family Practice Day.** Seattle. Tuesday. Group Health Central Campus. Contact: Marilyn Russell, 201 16th Ave., East, Seattle, WA 98112. (206) 326-7349.

June 23-27—**(OREGON) Modern Medical Practice.** Ashland. Wednesday-Sunday. Ashland Inn. Contact: U/W.

June 24-25—**EKG Interpretation and Arrythmias.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

June 24-26—**Scientific Aspects of Dance.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact: U/W.

June 28—**Recent Advances in Hematology.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

July 15-16—**Surviving the Elements.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

July 23—**Marriage of the Professional.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

(Continued on Page 68)

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

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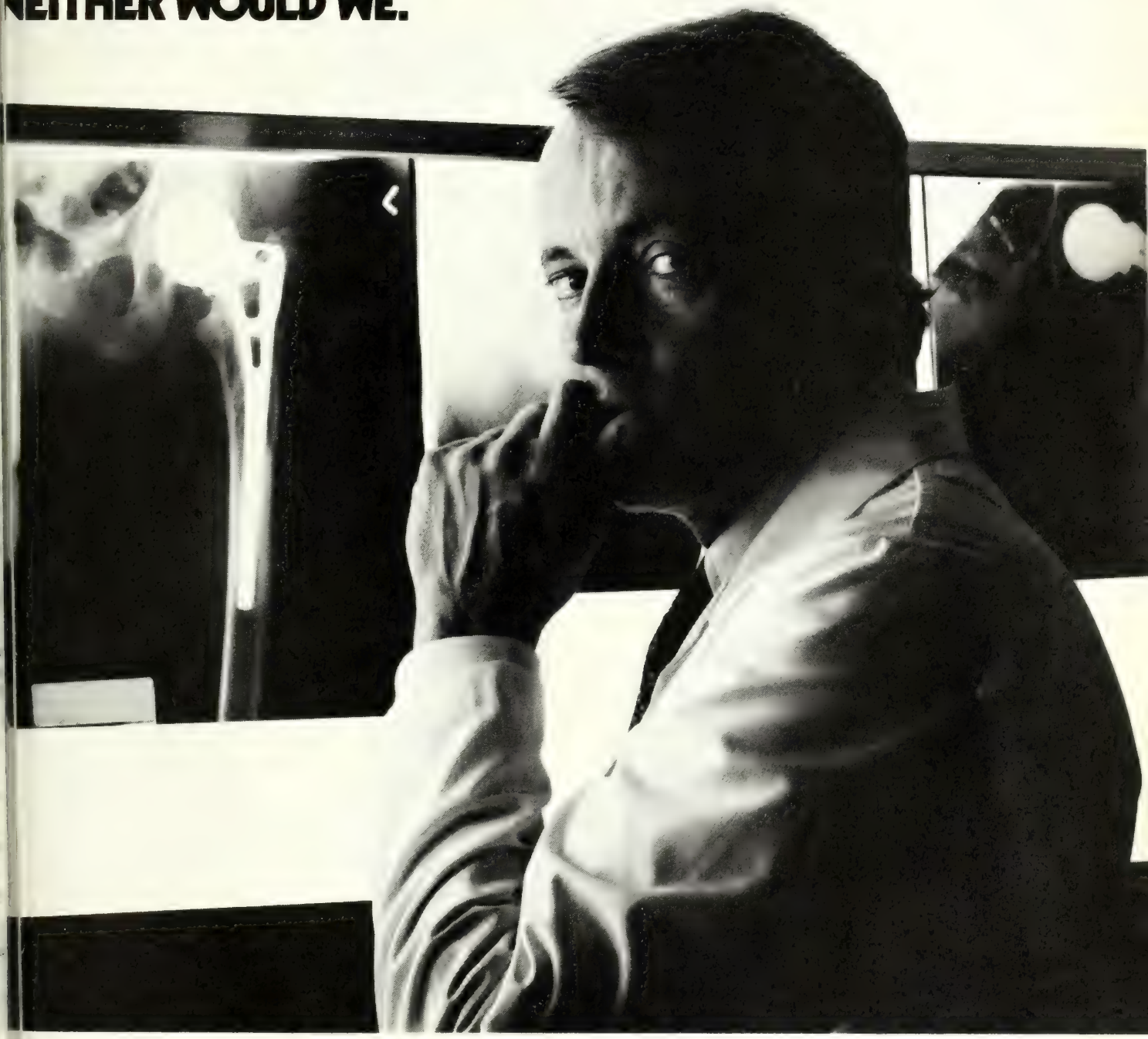

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WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: June 6-8, 1982, Chena Hot Springs.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. House of Delegates' Annual Meeting: May 28-29, 1982, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 11-16, 1983, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 21-24, 1982, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 11-14, 1982, Hilton Hawaiian Village, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 28-31, 1982, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 30-November 2, 1982, Sheraton, Great Falls.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 14-16, 1982, MGM Grand Hotel, Reno.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. Annual Meeting: May 5-7, 1982, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: November 3-5, 1982, Thunderbird, Jantzen Beach.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: September 14-17, 1982, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 7-10, 1982, Towne Motel, Yakima.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 30-July 3, 1982, Jackson Lake Lodge, Moran.

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July 23-25—**Washington State Society of Anesthesiologists: Seafair IV Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center. Contact: VMMC.

July 30-31—**Infertility.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

August 19-21—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

September 8-15—**13th International Cancer Congress.** Seattle. Wednesday-Wednesday. Seattle Center. Contact: Congress Operations Office, 13th International Cancer Congress, Fourth and Blanchard Building, Suite 1800, Seattle, WA 98121. (206) 621-9440.

September 16-18—**(WYOMING) Cytology Continuing Education Workshop.** Jackson. Thursday-Saturday. Contact: CME Harborview.

September 23-25—**Cytology Continuing Education Workshop.** Renton. Thursday-Saturday. Valley General Hospital. Contact: CME Harborview.

October 7-10—**Annual Meeting, Washington State Medical Association.** Yakima. Thursday-Sunday. Yakima Convention Center, The Towne Plaza, and The Holiday Inn. Contact: Marcia Wahlman, Convention Coordinator, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

November 11-12—**Topics in Emergency Medicine.** Seattle. Thursday-Friday. Sea-Tac Marriott Hotel. Contact: Heidi Hilby, Executive Secretary, Washington Chapter, American College of Emergency Physicians, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

WYOMING

June 30-July 3—**Wyoming Medical Society Annual Meeting.** Moran. Wednesday-Saturday. Jackson Lake Lodge. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne. WY 82001. (307) 635-2424.

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onoamine oxidase (MAO) inhibitors or within 14 days
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ic crises, severe convulsions and deaths have occurred
th concomitant use, then initiate cautiously, gradually
creasing dosage until optimal response is achieved
ntraindicated during acute recovery phase following
yocardial infarction
arnings: Use with great care in patients with history of
nary retention or angle-closure glaucoma. Severe con-
pation may occur in patients taking tricyclic antidepres-
nts and anticholinergic-type drugs. Closely supervise
rdiovascular patients. (Arrhythmias, sinus tachycardia
d prolongation of conduction time reported with use of
yclic antidepressants, especially high doses. Myocar-
l infarction and stroke reported with use of this class of
gs.) Caution patients about possible combined effects
h alcohol and other CNS depressants and against haz-
ous occupations requiring complete mental alertness
g., operating machinery, driving.)
***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
e physical and psychological dependence to chlor-
epoxide have been reported rarely, use caution in
inistering Limbitrol to addiction-prone individuals or
e who might increase dosage. withdrawal symptoms
wing discontinuation of either component alone have
n reported (nausea, headache and malaise for amitrip-
e symptoms [including convulsions] similar to those
arbiturate withdrawal for chlordiazepoxide)
autions: Use with caution in patients with a history
izures, in hyperthyroid patients or those on thyroid
cation, and in patients with impaired renal or hepatic
ion. Because of the possibility of suicide in depressed
nts, do not permit easy access to large quantities in
patients. Periodic liver function tests and blood
's are recommended during prolonged treatment
iptyline component may block action of guanethidine
milar antihypertensives. Concomitant use with other
notropic drugs has not been evaluated. sedative
s may be additive. Discontinue several days before
ry. Limit concomitant administration of ECT to essen-
eatment. See Warnings for precautions about preg-
y. Limbitrol should not be taken during the nursing
d. Not recommended in children under 12. In the
y and debilitated, limit to smallest effective dosage to
ide ataxia, oversedation, confusion or anticholinergic
s.
se Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely. The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.
Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses; for patients who do not tolerate higher doses.
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For broad symptom response, including insomnia

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In the treatment of insomnia

Good mornings start with restful nights.

Dalmane *(flurazepam HCl/Roche)* patients fall asleep faster, sleep longer and seldom awaken with morning hangover.

Feeling well rested in the morning usually means having slept well the night before. And for insomniac patients receiving hypnotic therapy, a good morning also means awakening with few side effects from their medication. Many physicians choose Dalmane for their patients who suffer from insomnia for this very reason.

Aside from enabling patients to fall asleep more quickly and sleep longer, Dalmane seldom causes morning hangover. Most Dalmane patients feel alert and refreshed when they awaken. In 53 paired-night clinical studies comparing Dalmane and placebo in 2010 insomniac patients with a variety of secondary diagnoses, most Dalmane patients awakened more alert and refreshed, and less groggy and drowsy, than on nights when they had taken only placebo.[1] In a double-blind crossover study of 42 patients in private practice, approximately three tir as many patients reported feeling refreshed and alert u awakening after a night on Dalmane (flurazepam/Ro compared to placebo nights.[2] This difference was high significant ($p<0.001$). And a retrospective study of 2 hospitalized patients who received Dalmane revealed a 3.1% incidence of side effects.[3]

While residual effects from Dalmane therapy are infrequent, patients should be cautioned about drinkin alcohol, driving or operating hazardous machinery aft ingesting the drug.

Efficacy and safety in a broad range of patient types.

Over 2000 clinical trials involving more than 10,000 patients have shown that Dalmane patients f asleep sooner, sleep longer and experience fewer noct awakenings.[4] The safety and efficacy of Dalmane hav been demonstrated in medical and surgical hospitalize patients, in patients seen in office practice and in elde patients.[5-8] Since the risk of oversedation, dizziness, c

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sion and/or ataxia increases with larger doses in the elderly, it is recommended that the dosage be limited to 15 mg.

Moreover, the efficacy and safety of Dalmane for the treatment of insomnia have been demonstrated in thousands of patients with a variety of primary medical conditions, including cardiovascular, neuropsychiatric, endocrine-metabolic, gastrointestinal, genitourinary, respiratory and musculoskeletal disorders.[1] Dalmane (flurazepam HCl/Roche) is contraindicated in pregnancy and in patients hypersensitive to the drug.

Avoids rebound insomnia upon discontinuation.

Rebound insomnia—a worsening of sleep beyond pretherapy levels after drug discontinuation—has been reported as a potential clinical problem with some hypnotics.[9,10] However, this problem has not been reported with Dalmane. In eight out of eight sleep laboratory studies, there were no reports of rebound insomnia.[11] When you prescribe Dalmane, you can be confident of efficacy that enhances therapeutic progress. Your insomniac patients can be assured of a restful night, night after night—a good start for a good morning.

References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **2.** Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971. **3.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **4.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **5.** Meyer JA, Kurland KZ: *Milit Med 138*:471-474, Aug 1973. **6.** Feffer HL, Gibbons B: *Med Times 101*(8):130-135, Aug 1973. **7.** Jacobson A *et al*: *Psychophysiology 7*:345, Sep 1970. **8.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **9.** Kales A, Scharf MB, Kales JD: *Science 201*:1039-1041, Sep 1978. **10.** Kales A *et al*: *JAMA 241*:1692-1695, Apr 1979. **11.** Monti JM: *Methods Find Exp Clin Pharmacol 3*(5):303-326, 1981

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15-mg/30-mg capsules

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stands apart

Please see following page for summary of product information.

Dalmane®
flurazepam HCl/Roche
15 mg, 30 mg capsules

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.

Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg recommended initially until response is determined.

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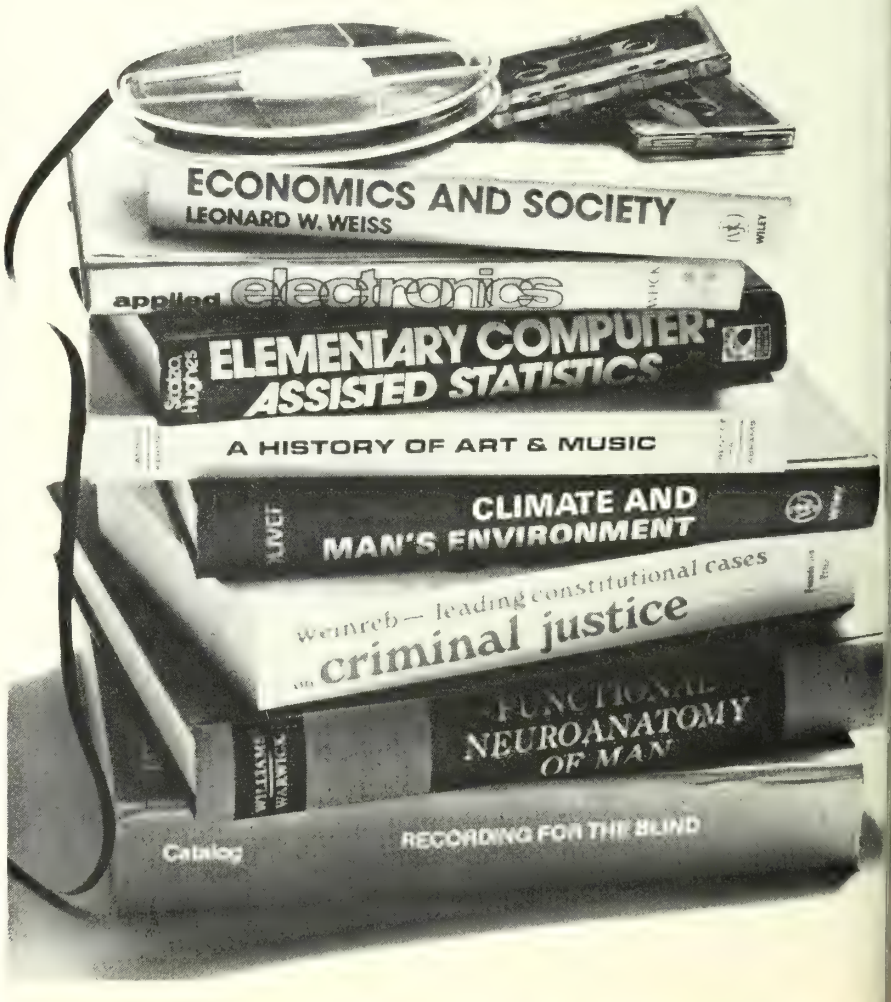

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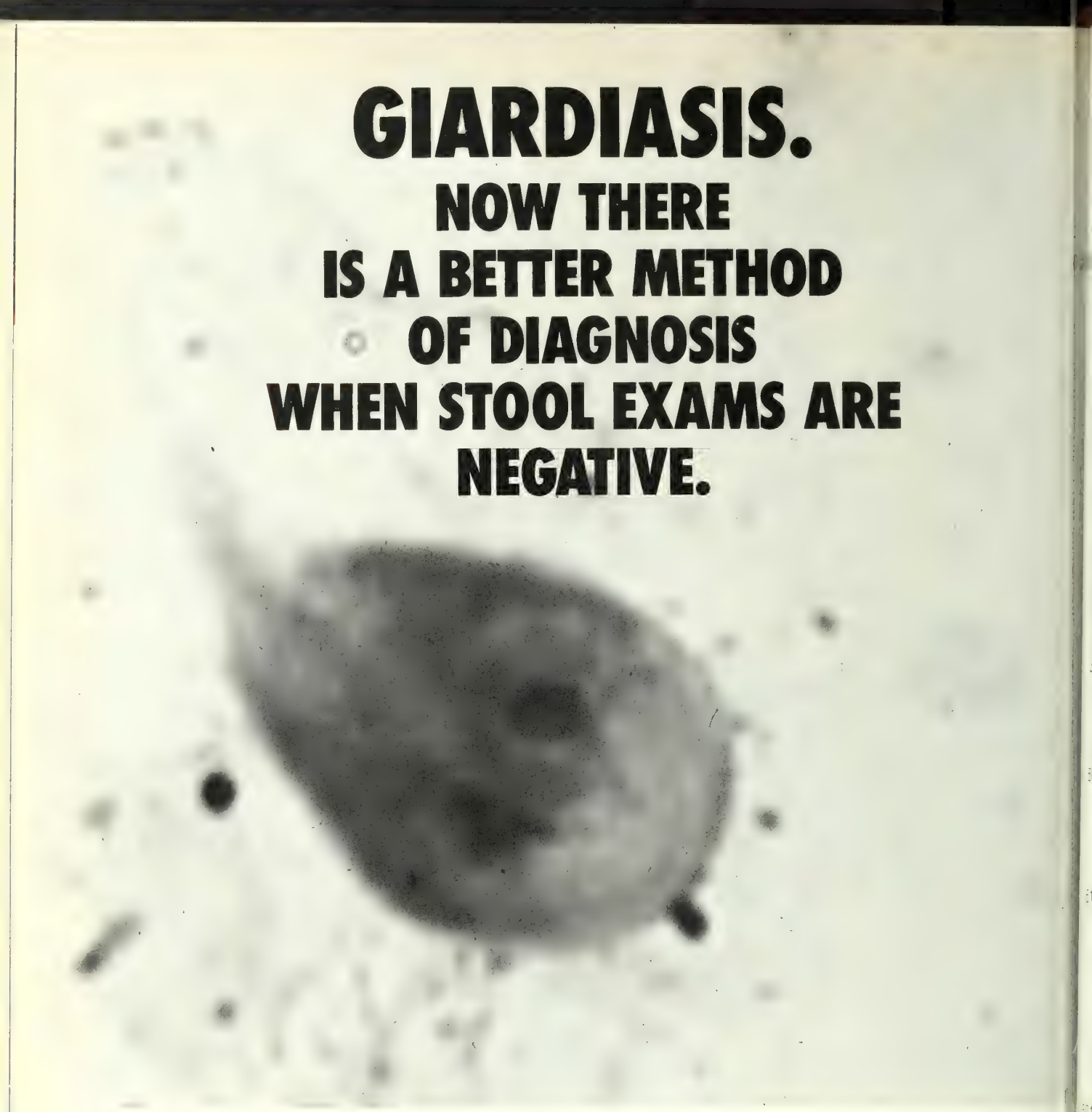

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Rosenthal, P., and Liebman, W.M: Comparative study of stool examinations, duodenal aspiration and pediatric Entero-Test for giardiasis in children. *J. PEDIAT. 96:* 278 (Feb.) 1980.

Thomas, G. E., et al: Use of the Entero-Test duodenal capsule in the diagnosis of giardiasis. *South Afr. Med J. 48:* 2219, 1974.

Lopez, M. E., et al: Infeccion duodeno-yeyunal en el niño con desnutricion energetico-proteinica. *Rev. Med. Hosp. Nat. Niños 13:* 53, 1978.

Gilman, R. H: Identification of gall typhoid carriers by a string bladder device. *The Lancet:* April 14, p. 795, 1979.

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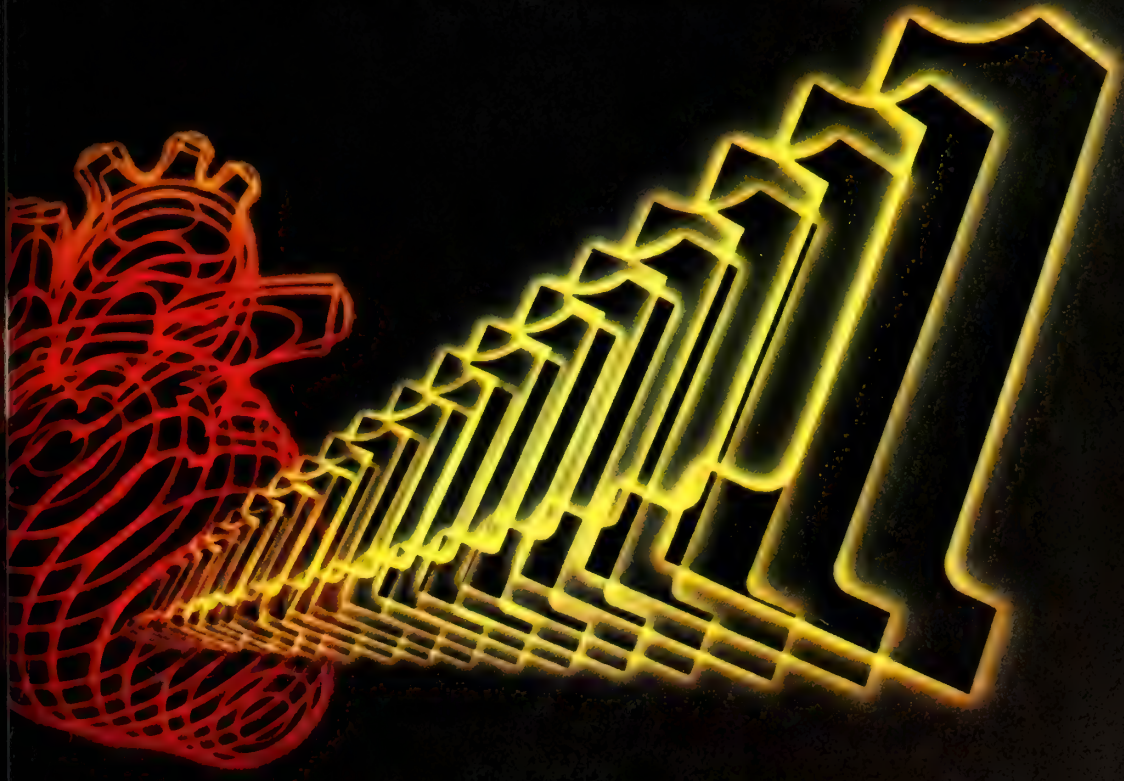

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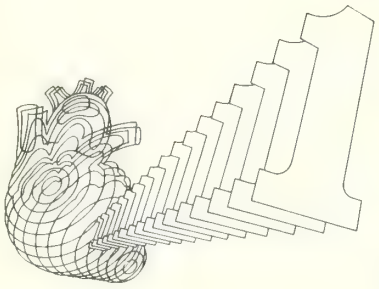

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WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occur commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

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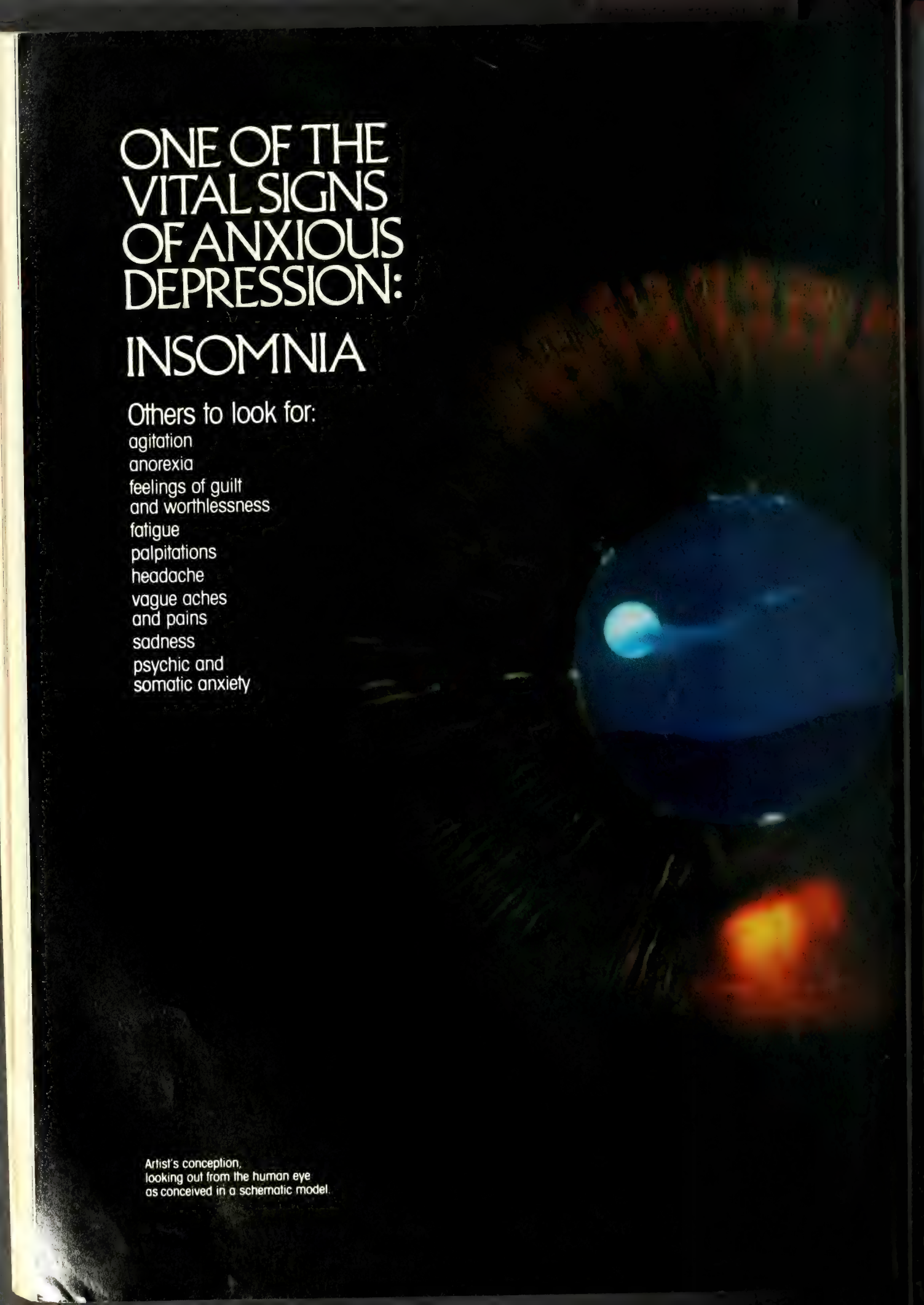

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).
***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated. Sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
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Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms; syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly. Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.
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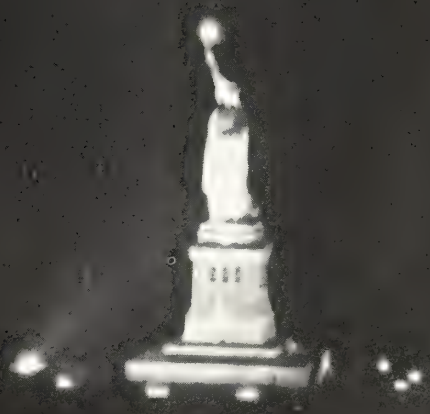

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023-2

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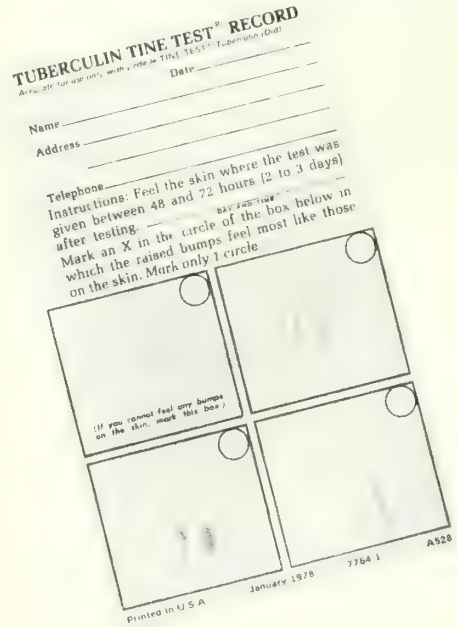
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Instructions: Feel the skin where the test was given between 48 and 72 hours (2 to 3 days) after testing.
Mark an X in the circle of the box below in which the raised bumps feel most like those on the skin. Mark only 1 circle.
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A528

...and no easier method to confirm the results.

Lederle Tuberculin, Old, TINE TEST®

Indications: For screening for tuberculosis.

Precautions: Use with caution in persons with acute tuberculosis (activation of quiescent lesions is rare); and in patients with known allergy to acacia. Reactivity to the test may be suppressed in those receiving corticosteroids or immunosuppressive agents, or those who have recently been vaccinated with live virus vaccine such as measles, mumps, rubella, polio, etc. With a positive reaction, further diagnostic procedures must be considered, i.e., chest x-ray, microbiologic examinations of sputum and other specimens, confirmation of positive tine test (except vesiculation reactions) by Mantoux method. When vesiculation occurs, the reaction is to be interpreted as strongly positive and a repeat test by the Mantoux method must not be attempted. If a patient has a history of occurrence of vesiculation and necrosis with a previous tuberculin test by any method, tuberculin testing should be avoided. Similar or more severe vesiculation with or without necrosis is likely to occur.

Pregnancy Category C. Animal reproduction studies have not been conducted; whether Tuberculin, Old, TINE TEST® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity is unknown. Tuberculin, Old, TINE TEST should be given to a pregnant woman only if clearly needed. During pregnancy, known positive reactors may demonstrate a negative response.

Adverse Reactions: Vesiculation, ulceration, or necrosis may appear at test site in highly sensitive persons. Pain, pruritus and discomfort at test site may be relieved by cold packs or by topical glucocorticoid ointment or cream. Any transient bleeding at puncture site is not significant.

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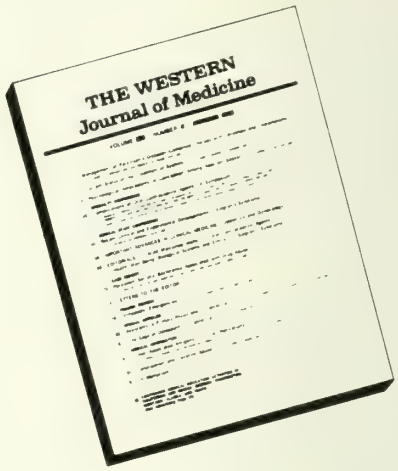

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(PIROXICAM) 20 mg capsules

ONE CAPSULE ONCE DAILY

FOR OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

see next page for FELDENE (piroxicam) prescribing information

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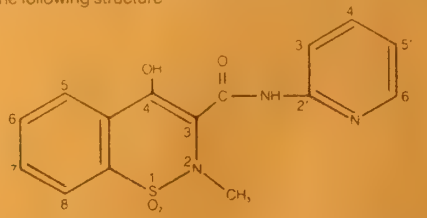
FELDENE® CAPSULES
(piroxicam)
For Oral Use

DESCRIPTION. FELDENE (piroxicam) is 4-Hydroxy-2-methyl-*N*-2 pyridinyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, an oxicam. Members of the oxicam family are not carboxylic acids, but they are acidic by virtue of the enolic 4-hydroxy substituent. FELDENE occurs as a white crystalline solid, sparingly soluble in water, dilute acid and most organic solvents. It is slightly soluble in alcohols and in aqueous alkaline solution. It exhibits a weakly acidic 4-hydroxy proton (pKa 5.1) and a weakly basic pyridyl nitrogen (pKa 1.8). It has the following structure



Molecular Formula: $C_{15}H_{13}N_3O_4S$ Molecular Weight: 331.35

CLINICAL PHARMACOLOGY. FELDENE has shown anti-inflammatory, analgesic and antipyretic properties in animals. Edema, erythema, tissue proliferation, fever, and pain can all be inhibited in laboratory animals by the administration of FELDENE. It is effective regardless of the etiology of the inflammation. The mode of action of FELDENE is not fully established at this time. However, a common mechanism for the above effects may exist in the ability of FELDENE to inhibit the biosynthesis of prostaglandins, known mediators of inflammation.

It is established that FELDENE does not act by stimulating the pituitary-adrenal axis.

FELDENE is well absorbed following oral administration. Drug plasma concentrations are proportional for 10 and 20 mg doses, generally peak within three to five hours after medication, and subsequently decline with a mean half-life of 50 hours (range of 30 to 86 hours, although values outside of this range have been encountered).

This prolonged half-life results in the maintenance of relatively stable plasma concentrations throughout the day on once daily doses and to significant drug accumulation upon multiple dosing. A single 20 mg dose generally produces peak piroxicam plasma levels of 1.5 to 2 mcg/ml, while maximum drug plasma concentrations, after repeated daily ingestion of 20 mg FELDENE, usually stabilize at 3-8 mcg/ml. Most patients approximate steady state plasma levels within 7 to 12 days. Higher levels, which approximate steady state at two to three weeks, have been observed in patients in whom longer plasma half-lives of piroxicam occurred.

FELDENE and its biotransformation products are excreted in urine and feces, with about twice as much appearing in the urine as the feces. Metabolism occurs by hydroxylation at the 5 position of the pyridyl side chain and conjugation of this product; by cyclodehydration; and by a sequence of reactions involving hydrolysis of the amide linkage, decarboxylation, ring contraction, and N-demethylation. Less than 5% of the daily dose is excreted unchanged.

Concurrent administration of aspirin (3900 mg/day) and FELDENE (20 mg/day), resulted in a reduction of plasma levels of piroxicam to about 80% of their normal values. The use of FELDENE in conjunction with aspirin is not recommended because data are inadequate to demonstrate that the combination produces greater improvement than that achieved with aspirin alone and the potential for adverse reactions is increased. Concomitant administration of antacids had no effect on FELDENE plasma levels. The effects of impaired renal function or hepatic disease on plasma levels have not been established.

FELDENE, like salicylates and other nonsteroidal anti-inflammatory agents, is associated with symptoms of gastrointestinal tract irritation (see ADVERSE REACTIONS). However, in a study utilizing ^{51}Cr-tagged red blood cells, 20 mg of FELDENE administered as a single dose for four days did not result in a significant increase in fecal blood loss and did not detectably affect the gastric mucosa. In the same study a total daily dose of 3900 mg of aspirin, i.e., 972 mg q.i.d., caused a significant increase in fecal blood loss and mucosal lesions as demonstrated by gastroscopy.

In controlled clinical trials, the effectiveness of FELDENE has been established for both acute exacerbations and long-term management of rheumatoid arthritis and osteoarthritis.

The therapeutic effects of FELDENE are evident early in the treatment of both diseases with a progressive increase in response over several (8-12) weeks. Efficacy is seen in terms of pain relief and, when present, subsidence of inflammation.

Doses of 20 mg/day FELDENE display a therapeutic effect comparable to therapeutic doses of aspirin, with a lower incidence of minor gastrointestinal effects and tinnitus.

FELDENE has been administered concomitantly with fixed doses of gold and corticosteroids. The existence of a "steroid-sparing" effect has not been adequately studied to date.

INDICATIONS AND USAGE. FELDENE is indicated for acute or long-term use in the relief of signs and symptoms of the following:

1. osteoarthritis
2. rheumatoid arthritis

Dosage recommendations for use in children have not been established.

CONTRAINDICATIONS. FELDENE should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other anti-inflammatory agents.

WARNINGS. In controlled clinical trials incidence of peptic ulceration with the maximum recommended FELDENE capsule dose of 20 mg/day was 0.8%. The use of doses higher than the recommended dose is associated with an increase in the incidence of gastrointestinal irritation and ulcers. As with other nonsteroidal anti-inflammatories, the administration of FELDENE to patients with a history of upper gastrointestinal tract disease should be closely supervised.

PRECAUTIONS. As with other anti-inflammatory agents, long-term administration to animals results in renal papillary necrosis and related pathology in rats, mice, and dogs.

As with other drugs that inhibit prostaglandin biosynthetase, reversible elevations of BUN have been reported in clinical studies with FELDENE. The effect is thought to result from inhibition of renal prostaglandin synthesis resulting in a change in medullary and deep cortical blood flow with an attendant effect on renal function. Because of the extensive renal excretion of piroxicam, patients with impaired renal function should be carefully monitored.

Although other non-steroidal anti-inflammatory drugs do not have the same direct effects on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree, therefore, patients who may be adversely affected by such an action should be carefully observed when FELDENE is administered.

Because of reports of adverse eye findings with non-steroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

Less than 1.0% of patients receiving FELDENE (piroxicam) have shown reversible elevation of one or more liver function parameters. While concurrent alcohol may have been involved in some of these changes, a relationship to FELDENE could not be excluded. Studies in patients with impaired liver function have not been done.

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur (see CLINICAL PHARMACOLOGY), about 4% of the patients treated with FELDENE alone or concomitantly with aspirin had reductions in hemoglobin and hematocrit values were observed. Therefore, these values should be determined if signs or symptoms of anemia occur.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, as with other nonsteroidal anti-inflammatory drugs, FELDENE should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposing to fluid retention.

DRUG INTERACTIONS. FELDENE is highly protein bound, and therefore might be expected to displace other protein-bound drugs. Although *in vitro* studies have shown this not to occur with dicoumarol, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels (see CLINICAL PHARMACOLOGY).

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the anti-toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam increased the incidence of dystocia and delayed parturition in pregnant animals when piroxicam administration was continued at pregnancy. Gastrointestinal tract toxicity was increased in pregnant females in the third trimester of pregnancy compared to nonpregnant females or females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS. The incidence of adverse reactions to piroxicam is based on clinical trials involving approximately 2300 patients, about 400 of whom were treated more than one year and 170 for more than two years. About 30% of all patients receiving daily doses of 20 mg of FELDENE experienced side effects. Gastrointestinal symptoms were the most prominent side effects—occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy for an overall incidence of peptic ulceration of about 1%.

Other than the gastrointestinal symptoms, edema, dizziness, headache, changes in hematological parameters, and rash have been reported in a small percentage of patients. Routine ophthalmoscopy and slit-lamp examinations have revealed no evidence of ocular changes in 205 patients followed from 3 to 24 months while on therapy.

Adverse reactions are listed below by body system for all patients in clinical trials of FELDENE at doses of 20 mg/day.

Incidence Greater Than 1% The following adverse reactions occurred more frequently than 1 in 100:

Gastrointestinal: stomatitis, anorexia, epigastric distress*, nausea*, constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, and indigestion.

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), leucopenia, eosinophilia.

Urogenital: BUN elevations (see PRECAUTIONS)

Central Nervous System: dizziness, somnolence, vertigo

Special Senses: tinnitus

Body as a Whole: headache, malaise

Cardiovascular/Respiratory: edema (see PRECAUTIONS)

Dermatologic: pruritus, rash

*Reactions occurring in 3% to 6% of patients treated with FELDENE.

Incidence Less Than 1% (Causal Relationship Probable)
The following adverse reactions occurred less frequently than 1 in 100. The probable exists that there is a causal relationship between FELDENE and these reactions:

Gastrointestinal: liver function abnormalities (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, dry mouth

Hematological: thrombocytopenia

Dermatologic: sweating, erythema, bruising, desquamation, erythema multiforme, epidermal necrolysis, Stevens-Johnson syndrome

Special Senses: swollen eyes, blurred vision, eye irritations

Body as a Whole: pain (colic)

Cardiovascular/Respiratory: hypertension (see PRECAUTIONS)

Urogenital: hematuria

Metabolic: hypoglycemia, weight increase, weight decrease

Central Nervous System: depression, insomnia, nervousness

Incidence Less Than 1% (Causal Relationship Unknown)
Other adverse reactions were reported with a frequency of less than 1 in 100, but a relationship between FELDENE and the reaction could not be determined.

Cardiovascular/Respiratory: palpitations, dyspnea

Central Nervous System: akathisia

Urogenital System: dysuria

OVERDOSAGE. In the event treatment for overdosage is required, the long plasma half-life (see CLINICAL PHARMACOLOGY) of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of several aspects and recommendation of specific antidotal efficacy at this time. It is reasonable to assume, however, that the standard measures of gastric evacuation and general support of therapy would apply.

ADMINISTRATION AND DOSAGE. Rheumatoid Arthritis, Osteoarthritis:
It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided. Because of the long half-life, FELDENE steady-state blood levels are not reached for 7-12 days. Therefore, although the therapeutic effects of FELDENE are evident early in treatment, there is a progressive increase in response over several weeks and the effect of therapy should not be assessed for two weeks.

Dosage recommendations and indications for use in children have not been established.

HOW SUPPLIED. FELDENE Capsules are available for oral administration as 10 mg (NDC 0069-3220-66) maroon and blue #322, and 20 mg (NDC 0069-3230-66) maroon #323, bottles of 100.

Unit dose 20 mg (NDC 0069-3230-41) packages of 100.

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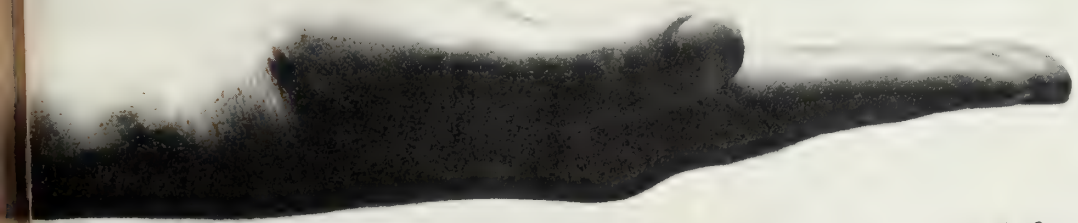

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June 17-19—**Cosmetic Blepharoplasty Workshop.** Jules Stein Eye Institute, Los Angeles. Thursday-Saturday. 24 hrs. $250. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

June 18—**Symposium on Gynecologic Oncology.** Alta Bates Hospital, Berkeley. Friday. 7 hrs. $75. Contact: Med. Ed. Dept., Alta Bates Hosp., 3001 Colby St., Berkeley 94705. (415) 845-7110, ext. 2055.

June 19-26—**Medical and Surgical Management of Ocular Inflammation.** USC at Mauna Kea Beach Hotel, Kamuela. One week. 26½ hrs. $435.

June 20-25—**Pathology of the Lung.** UCSD at Village Inn, La Jolla. Sunday-Friday. 50 hrs. $600.

June 21-25—**The Management of Contemporary Problems in Private Psychiatry.** USC at Vacation Village, San Diego. Monday-Friday. 21 hrs. $250.

June 24-26—**Practical Closed Circuit Anesthesia II.** Pacific Medical Center at Hyatt at Union Square, San Francisco. Thursday-Saturday. 17 hrs. $300. Contact: Office of Cont. Ed., PMC, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

June 24-27—**Golden State Medical Association—15th Annual Convention.** Sahara Hotel, Las Vegas. Thursday-Sunday. 13 hrs. Contact: Lillian Fortier, GSMA, P.O. Box 2151-Station A, Berkeley 94702. (415) 839-3466.

June 25-26—**Medical Aspects of Sexual Orientation: Medical and Psychological Issues.** Bay Area Physicians for Human Rights at S.F. Medical Society Bldg., San Francisco. Friday-Saturday. 10 hrs. Contact: James Krajeski, MD, 2001 Union St., San Francisco 94123. (415) 673-3189.

June 25-27—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Newporter Inn, Newport Beach. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

June 26—**Binge Eating and Purging: Recognition and Management of Bulimia.** UCLA. Saturday. 6 hrs. $80.

June 28-July 2—**Topics in Emergency Medicine.** UCSF. Monday-Friday. 35 hrs. $350.

July 6-8—**Family Practice Board Review Course.** UCSF. Tuesday-Thursday.

July 9-11—**Sensory Systems' Influence on Movement and Tone.** UCSD at Holiday Inn at the Embarcadero, San Diego. Friday-Sunday. 13 hrs. $180.

July 10-18—**30th Annual Intensive Review of Internal Medicine.** USC. 9 days. 57 hrs. $450.

July 11-12—**Pediatric Seminar.** Calif. Chap. 2, American Academy of Pediatrics, at Disneyland Hotel, Anaheim. Sunday-Monday. 13 hrs. $200, members; $225, nonmembers. Contact: Calif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

July 14—**Special Problems in Geriatric Medicine.** LLU. Wednesday. 4 hrs.

July 16-17—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

July 17-24—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela. One week. 21 hrs. $325.

July 23-24—**Disaster Planning Symposium.** UCLA. Friday-Saturday.

July 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: Ellie Gutman, EMA, 2310 Mason St., San Francisco 94133. (415) 956-5900.

(Continued on Page 25)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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Please see Brief Summary of Prescribing Information on following page.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

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Propranolol hydrochloride (INDERAL®)	80 mg
Hydrochlorothiazide	25 mg

WARNING: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

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INDICATION: INDERIDE is indicated in the management of hypertension. (See boxed warning.)

CONTRAINDICATIONS: Propranolol hydrochloride (INDERAL®): Propranolol hydrochloride is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

Hydrochlorothiazide: Hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to this or other sulfonamide-derived drugs.

WARNINGS: Propranolol hydrochloride (INDERAL®): CARDIAC FAILURE. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely. a) If cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn. b) If tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA. Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. In patients with impaired renal function, cumulative effects of the drug may develop.

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

USE IN PREGNANCY: Propranolol hydrochloride (INDERAL®): The safe use of propranolol in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers. Thiazides appear in breast milk. If the use of the drug is deemed essential, the patient should stop nursing.

PRECAUTIONS: Propranolol hydrochloride (INDERAL®): Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements such as foods with a high potassium content.

Any chloride deficit is generally mild, and usually does not require specific treatment except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration, have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

ADVERSE REACTIONS: Propranolol hydrochloride (INDERAL®): *Cardiovascular*: bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with achin and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpu

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Hydrochlorothiazide: *Gastrointestinal*: anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea; constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis.

Central Nervous System: dizziness, vertigo, paresthesias, headache, xanthopsia.

Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic react

Other: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduce or therapy withdrawn.

DOSAGE AND ADMINISTRATION: The dosage must be determined by individual titration. (see boxed warning)

Hydrochlorothiazide is usually given at a dose of 50 to 100 mg per day. The initial dose of propranolol is 40 mg twice daily and it may be increased gradually until optimum blood pressure control is achieved. The usual effective dose is 160 to 480 mg per day.

One to two INDERIDE tablets twice daily can be used to administer up to 320 mg of propranolol and 100 mg of hydrochlorothiazide. For doses of propranolol greater than 320 mg the combination products are not appropriate because their use would lead to an excessiv dose of the thiazide component.

When necessary, another antihypertensive agent may be added gradually beginning wit 50 percent of the usual recommended starting dose to avoid an excessive fall in blood pressure.

OVERDOSAGE OR EXAGGERATED RESPONSE: The propranolol hydrochloride (INDERAL) component may cause bradycardia, cardiac failure, hypotension, or bronchospasm.

The hydrochlorothiazide component can be expected to cause diuresis. Lethargy of var ing degree may appear and may progress to coma within a few hours, with minimal depres sion of respiration and cardiovascular function, and in the absence of significant serum electrolyte changes or dehydration. The mechanism of central nervous system depression with thiazide overdosage is unknown. Gastrointestinal irritation and hypermotility can occu temporary elevation of BUN has been reported, and serum electrolyte changes could occu especially in patients with impairment of renal function.

TREATMENT: The following measures should be employed. GENERAL—If ingestion is, or may have been, recent, evacuate gastric contents taking care to prevent pulmonary aspira tion. BRADYCARDIA—Administer atropine (0.25 to 1.0 mg). If there is no response to vaga blockade, administer isoproterenol cautiously. CARDIAC FAILURE—Digitalization and diuretics. HYPOTENSION—Vasopressors, *e.g.*, levarterenol or epinephrine. BRONCHOSPASM—Administer isoproterenol and aminophylline. STUPOR OR COMA—Administer supportive therapy as clinically warranted. GASTROINTESTINAL EFFECTS—Though usually of short duration, these may require symptomatic treatment. ABNORMALITIES IN BUN AND/OR SERUM ELECTROLYTES—Monitor serum electrolyte levels and renal function; in stitute supportive measures as required individually to maintain hydration, electrolyte balance, respiration, and cardiovascular-renal function.

HOW SUPPLIED: *No. 474*—Each INDERIDE®-40/25 tablet contains 40 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 and 1,000. Also unit dose package of 100.

No. 476—Each INDERIDE®-80/25 tablet contains 80 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 and 1,000. Also in unit dose package of 100.

References: 1. Veterans Administration Cooperative Study Group on Antihypertensive Agents: J.A.M.A. *237*: 2303 (May 23) 1977. 2. Bravo, E.L., Tarazi, R.C., and Dustan, H.P.: N. Engl. J. Med. *292*: 66 (Jan. 9) 1975. 3. Hollifield, J.W., and Slaton, P.E.: Acta Med. Scand. [Suppl.] *647*: 67, 1981. 4. Holland, O.B., Nixon, J.V., and Kuhnert, L.: Am. J. Med. *70*: 762 (Apr.) 1981.

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(Continued from Page 21)

July 24-30—**Laboratory Medicine.** USC at Marriott Hotel, Maui. One week. 27 hrs. $435.

July 25-29—**National Medical Association—87th Annual Convention and Scientific Assembly.** Hilton, San Francisco. Sunday-Thursday. 40 hrs. Contact: Christine Miller, Prog. Dir., NMA, 1301 Pennsylvania Ave., NW, Washington, DC 20001. (202) 347-8598.

August 6-8—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Clouds-Cal Neva Resort, Lake Tahoe. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 7-14—**Radiology.** USC at Mauna Kea Beach Hotel, Kamuela. One week. 27 hrs.

August 9-13—**Postgraduate Institute for Emergency Room Physicians—Symposium II.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 33 hrs. $425.

August 11—**Back Pain.** LLU. Wednesday.

August 12-13—**National Institute for Care of the Elderly.** Univ. of Nevada-Reno School of Medicine at MGM Grand, Reno. Thursday-Friday. 12 hrs. Contact: Leanne Stone, Cont. Ed., Univ. of Nevada-Reno, Reno 89557. (702) 784-4046.

August 12-14—**Selection and Technique for Use of Muscle and Musculocutaneous Flaps in Reconstructive Surgery.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 20 hrs. $420.

August 13-14—**Sports Medicine.** Univ. of Nevada-Reno School of Medicine at MGM Grand, Reno. Friday-Saturday. 12 hrs. Contact: Leanne Stone, Cont. Ed., Univ. of Nevada-Reno, Reno 89557. (702) 784-4046.

August 13-15—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 13-17—**Clinical Neuroanesthesia Workshop.** UCSD at Village Inn, La Jolla. Friday-Tuesday. 24 hrs. $325.

August 14-25—**25th Annual Postgraduate Refresher Course.** USC at Honolulu and Maui. 12 days. 37 hrs. $425.

August 14-25—**Update: Surgery 1982.** USC at Honolulu and Maui. 12 days. 35 hrs. $425.

August 16-20—**Advanced Diving Medicine.** UCSF at San Diego. Monday-Friday.

August 20-22—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at Hyatt, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 21-22—**Hemodynamic Monitoring/Pulmonary Artery Catheterization—Hands-on Workshops.** Calif. Soc. of Anesthesiologists at Stanford. Saturday-Sunday. 15 hrs. $275, members; $325, nonmembers. Contact: CSA, Ed. Prog. Div., 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 23-September 3—**Intensive Residency in Occupational Medicine, Session I.** UCSF at Golden Gateway Holiday Inn, San Francisco. 12 days. 80 hrs. $1,000.

August 26-28—**Advances in Diagnostic Imaging.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 20½ hrs. $275.

August 29-September 3—**Family Practice Refresher Course.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday.

August 30-September 1—**Napa Valley Radiology Conference.** Sacramento Radiology Research and Education Fndn. and No. Calif. Radiological Soc. at Napa Valley. Monday-Wednesday. 18 hrs. $275. Contact: Michael H. Reid, PhD, MD, Prog. Dir., Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

August 30-September 4—**5th Comprehensive Nephrology Review Course.** UCLA at Marriott, Los Angeles. Monday-Saturday. 38½ hrs. $595.

September 8—**Current Concepts in Menopausal and Post-Menopausal Care.** LLU. Wednesday.

September 11—**9th Annual Radiology Symposium.** So. Calif. Permanente Medical Group and Kaiser Fndn. Hospitals at Beverly Hilton, Beverly Hills. Saturday. Contact: Doris McMath, SCPMG, Regional Dept. of Ed. and Research, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 12-25—**Temporal Bone Surgical Dissection Course.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, House Ear Inst., 256 S. Lake St., Los Angeles 90057.

September 13-17—**Postgraduate Institute for Emergency Room Physicians—Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 33 hrs. $425.

September 16-18—**Postgraduate Institute on Geriatrics.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

September 16-18—**4th Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Thursday-Saturday.

September 20-22—**Alcoholism Treatment, Cooperation or Competition.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. $190. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

September 21-22—**American Heart Association-Greater Los Angeles Affiliate—50th Anniversary Fall Symposium.** Hilton, Los Angeles. Tuesday-Wednesday. 11 hrs. $70. Contact: Marilyn Cowan, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

September 24-25—**Antigens and Immunotherapy: Present and Future.** Los Angeles and California Societies of Allergy and Clinical Immunology at Marriott, Newport Beach. Friday-Saturday. Contact: Warren Richards, MD, Allergy-Clinical Immunology Div., Childrens Hosp., P.O. Box 54700, Terminal Annex, Los Angeles 90054.

September 24-25—**Update in Internal Medicine—27th Annual Medical Symposium.** So. Calif. Permanente Medical Group and Kaiser Fndn. Hospitals at Century Plaza, Los Angeles. Friday-Saturday. Contact: Mark Anthony, SCPMG, Regional Dept. of Ed. and Research, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 25—**Clinical Ultrasound in Obstetrics and the Neonatal Period.** Sacramento Radiology Research and Education Fndn. and No. Calif. Radiological Soc. at Sacramento. Saturday. 6 hrs. $75. Contact: J. P. McGahan, MD, Prog. Dir., Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

September 28-October 1—**American College of Emergency Physicians.** San Francisco. Tuesday-Friday. Contact: Registrar, ACEP, P.O. Box 61911, Dallas 75261. (214) 659-0911.

September 29-30—**39th Annual Brennemann Memorial Lectures.** L.A. Pediatric Soc. at Hilton, Los Angeles. Wednesday-Thursday. 11 hrs. $145, members; $175, nonmembers. Contact: Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

September 29-October 1—**New Concepts in Maxillofacial Surgery.** STAN and Swiss Assn. for the Study of Internal Fixation at Stanford. Wednesday-Friday. 17 hrs. $400. Contact: ASIF Course Secretariat, P.O. Box 514, Wayne, PA 19087. (215) 293-0654.

September 30-October 2—**Pulmonary Update.** UCSF. Thursday-Saturday.

October 1-2—**Advances in Heart Disease, Aging, Diabetes and Cancer Research.** UCLA at Beverly Hilton, Beverly Hills. Friday-Saturday. Contact: Robert J. Morin, MD, Harbor-UCLA Medical Ctr., Torrance 90509. (213) 533-2233.

October 1-2—**Frontiers in Medicine: Implications for the Future.** UCLA at Beverly Hilton, Beverly Hills. Friday-Saturday. 16 hrs. $225.

October 1-2—**Intraocular Lens Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

October 1-2—**Mycology Review.** STAN. Friday-Saturday. 14

(Continued on Page 36)

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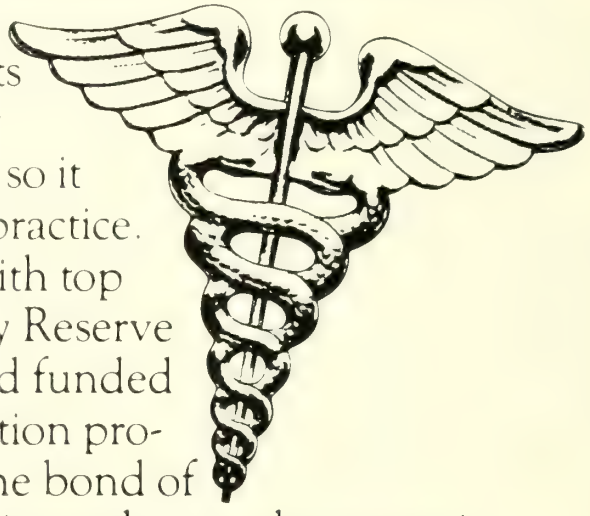

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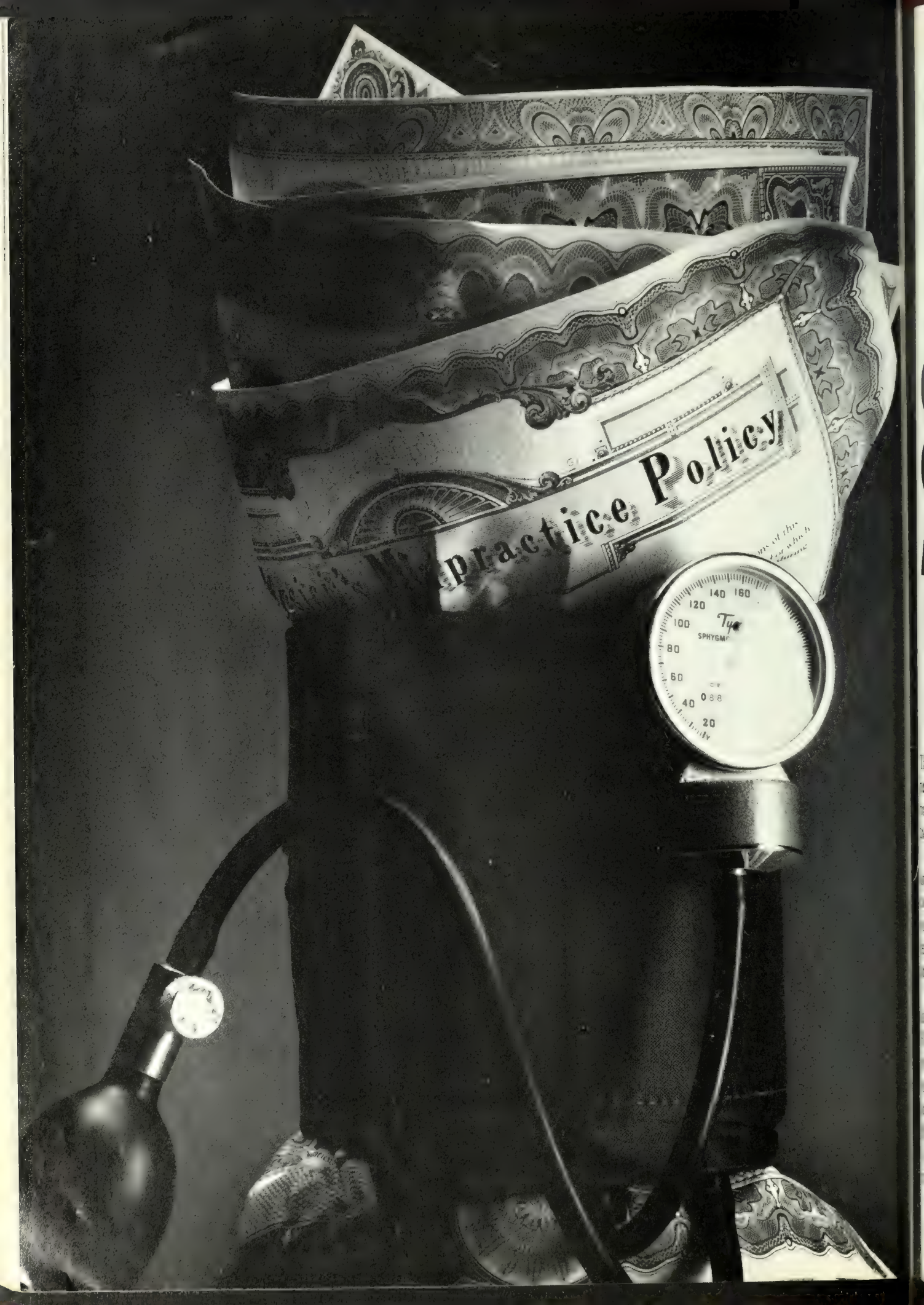
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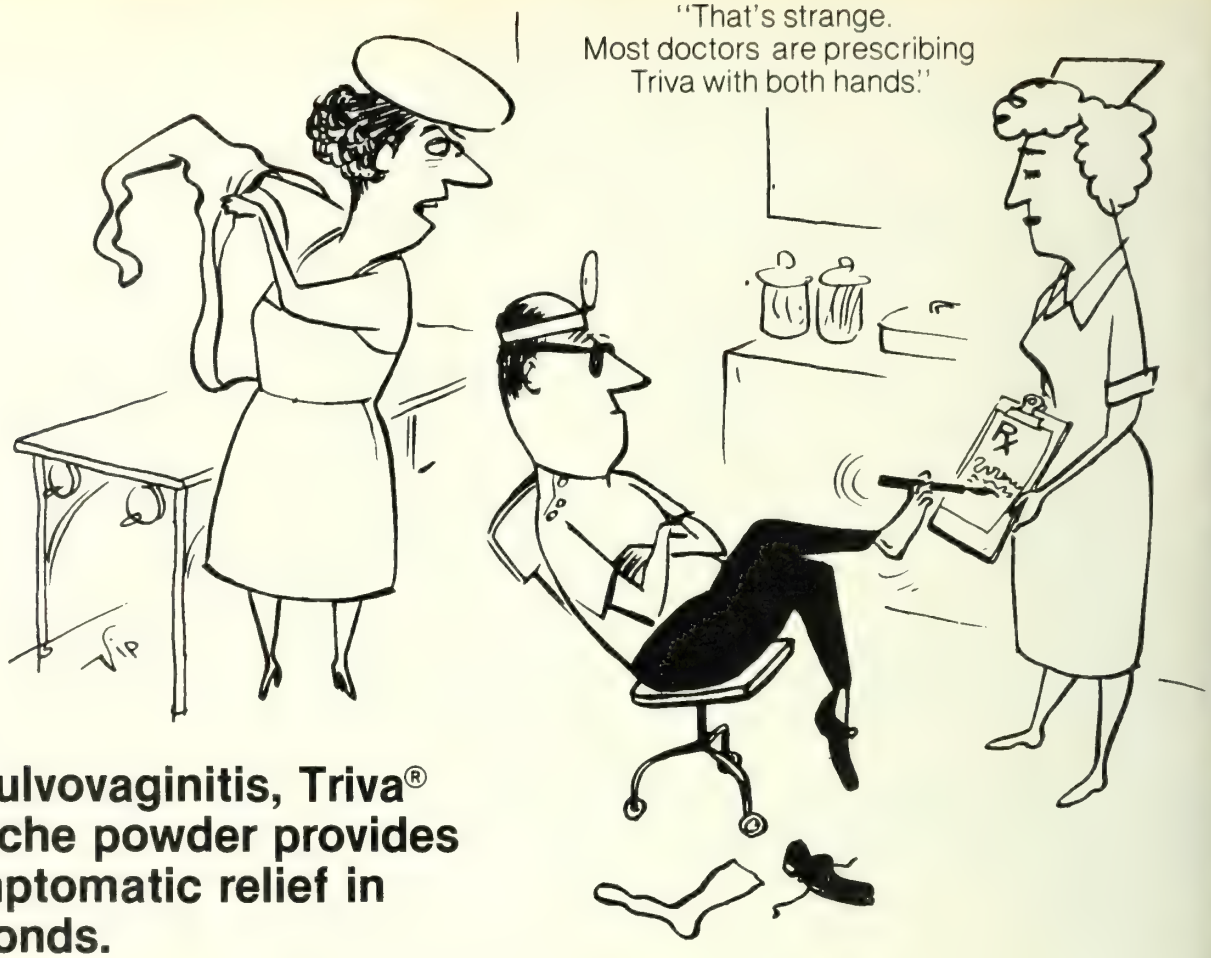

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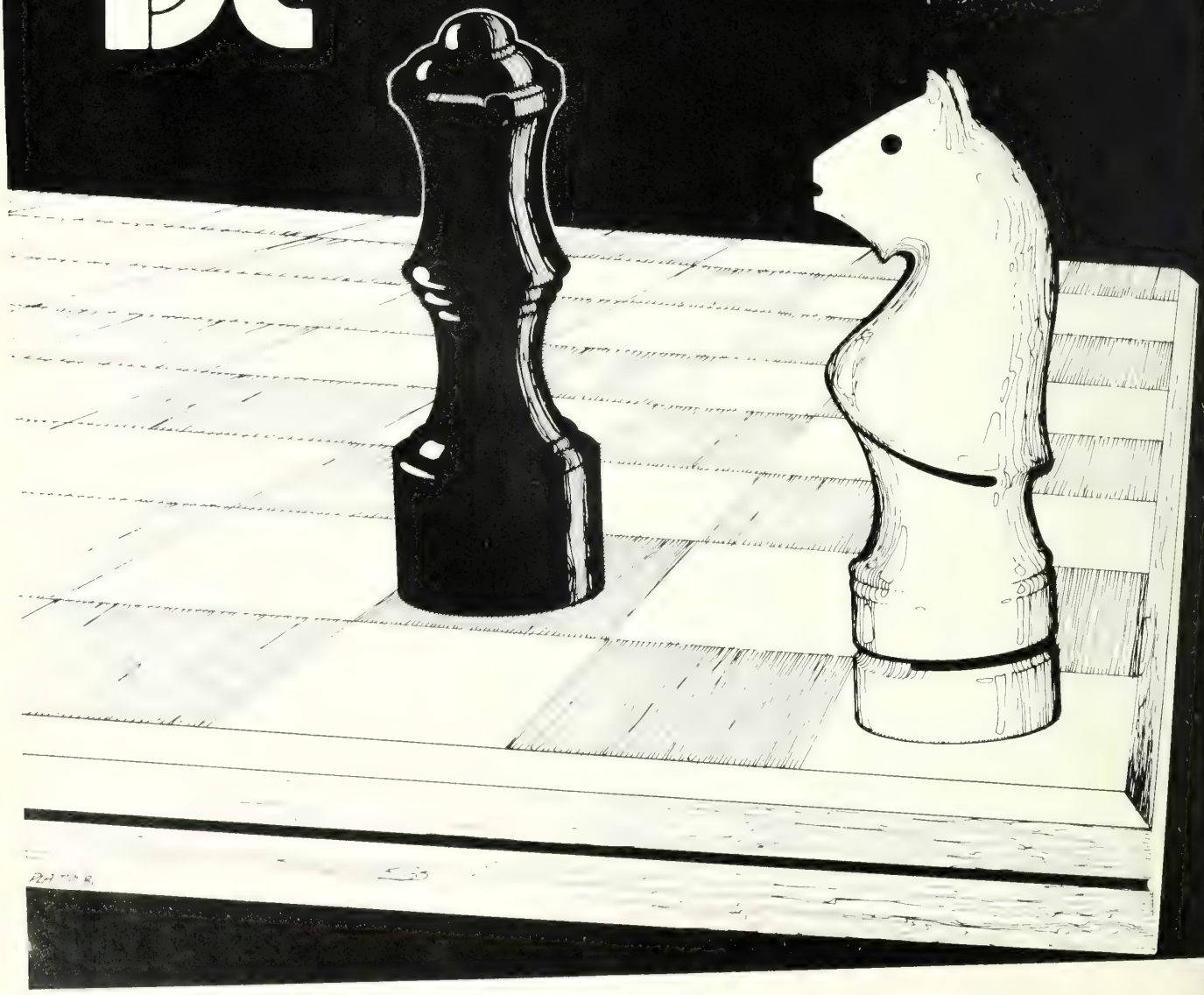

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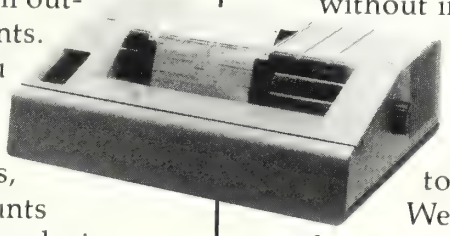

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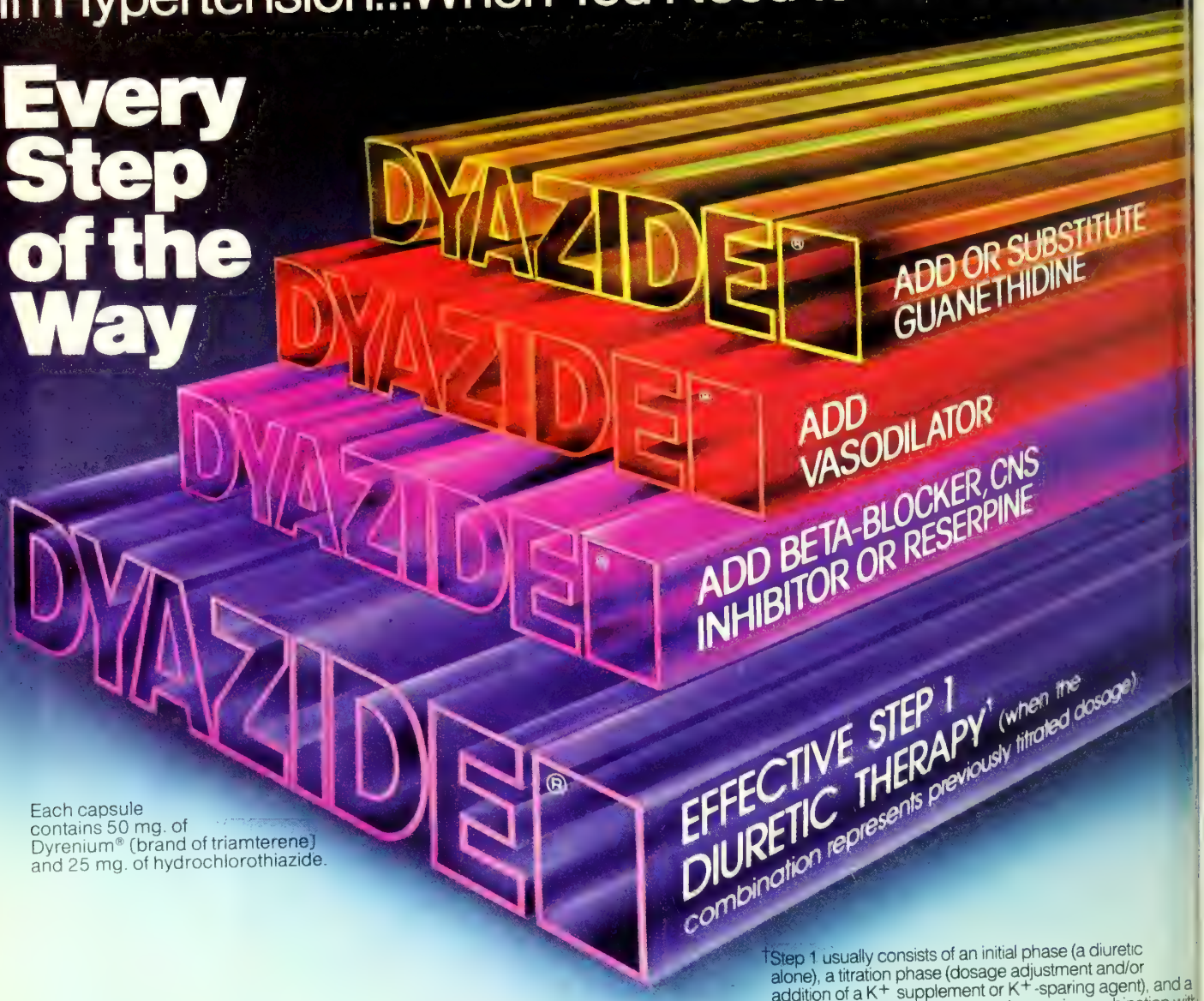

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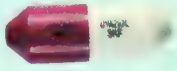

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Refer to: Ettinger B, Wingerd J: Thyroid supplements: Effect on bone mass. West J Med 1982 Jun; 136:473-476

Thyroid Supplements: Effect on Bone Mass

BRUCE ETTINGER, MD, *San Francisco, and* JOHN WINGERD, MA, *Oakland, California*

Thyrotoxicosis and thyroid replacement therapy can cause osteopenia. The relative effects of such therapy and of aging, body size, menopausal status and smoking on bone mass were compared by measuring the combined cortical thickness (CCT) of the second metacarpal bone in 151 women taking thyroid hormone. Age was the single factor strongly related to CCT, with the mean CCT decreasing by 0.045 mm per year. Women who had taken estrogen replacement medications had a higher CCT measurement, while those who used thyroid hormone in a dose of at least 3 grains a day had a lower CCT. The rate of loss was reduced in those women using estrogen replacement therapy and increased in those women taking 3 grains or more of thyroid hormone. Women taking 3 grains or more of thyroid hormone should be advised that they are at higher risk for osteopenia.

THYROTOXICOSIS CAUSES LOSS of bone mineral.[1-4] Thyroid hormone replacement therapy, often administered in supraphysiologic doses, may also contribute to osteopenia. We have assessed the relative contribution of age, body size, menopausal status, smoking and thyroid hormone therapy to osteopenia by measuring the combined cortical thickness (CCT) of the second metacarpal bone.

Subjects and Methods

White female volunteers, at least 35 years of age, who had regularly used a constant dosage of thyroid hormone supplements for more than five years were self-selected from the Kaiser-Permanente Medical Center, San Francisco, clinic population at the time of their multiphasic health examination.

Criteria for exclusion from the study were the following: chronic alcoholism, malabsorption syndrome, postgastrectomy state, chronic renal failure, hyperparathyroidism, arthritis or other conditions that would affect the bones of the hand and long-term use of phenytoin (Dilantin) or glucocorticoids.

A questionnaire and medical record review provided information regarding each woman's thyroid hormone use, age at menopause, postmenopausal estrogenic hormone use and smoking history, in addition to her usual adult weight and height. The use of 1 grain of desiccated thyroid was considered equivalent to taking 100 μg of levothyroxine. An x-ray film of the nondominant hand was taken with fine-grained, rapid-processing mammography film. Using a scaled magnifier,

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Submitted, revised, December 24, 1981.

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ABBREVIATIONS USED IN TEXT

CCT = combined cortical thickness
FT_4I = free thyroxine index
T_3 = triiodothyronine
T_4 = thyroxine

one of the authors (B.E.) measured within 0.1 mm CCT of the midshaft of the second metacarpal bone according to the method of Garn.[5] Duplicate readings were done without knowledge of the clinical status of the women. Serum thyroxine (T_4) was measured by solid-phase radioimmunoassay (normal range, 4.5 to 11.4 μg per dl) and serum triiodothyronine (T_3) uptake was measured using talc as the adsorber (normal range, 25 percent to 35 percent). Based on an analysis of 2,556 normal women,[6] the product of the T_4 and T_3 uptake, the free thyroxine index (FT_4I), did not exceed 380. Levels above 380 are invariably associated with hyperthyroidism, judged clinically and chemically.

Results

The precision of the CCT measurements was 3.6 percent, and replicate measurements of CCT agreed within 0.3 mm in 85 percent of the cases. The mean CCT measurements obtained in this study were within 1 percent of the values predicted for white women of the same age on the basis of the standards published by Virtama and Helelä and were 2 percent below the standards published by Garn.[5]

Table 1 summarizes the clinical data for 151 women, classified by their thyroid dosage. Desiccated thyroid was used by 73 percent of the groups taking 1 and 2 grains and by 90 percent of the groups taking 3 and 4 grains. A past history of hyperthyroidism existed in 3 percent of the women taking 1 and 2 grains and in 2 percent of the women taking 3 or 4 grains. Hypothyroidism was the reason given for physicians prescribing thyroid hormone in 77 percent of the 1- and 2-grain users and 67 percent of the 3- and 4-grain users. Several of the variables shown in Table 1 proved to be significantly related to CCT. These factors are, however, correlated with each other to varying degrees. Multiple regression analysis was used to measure the independent effects of each variable.

TABLE 1.—*Clinical Findings Related to Thyroid Hormone Use*

	Grains			
	1	*2*	*3*	*4*
Number of subjects ..	47	52	39	13
Mean CCT (mm) ...	4.28	4.64	4.32	4.28
Mean age (yr)	59.3	56.3	56.5	52.8
Mean height (in)	63.9	64.5	64.9	63.5
Mean weight (kg) ...	61.9	63.0	64.5	57.9
Smokers (%)	13	25	33	31
Postmenopausal (%) .	79	79	72	54
Mean age at menopause (yr) ...	47.6	47.2	47.0	43.1
Women using estrogen (%)*	34	33	28	31
Mean duration thyroid therapy (yr)	19.2	19.3	20.5	19.2
FT_4I	242	289	293	340

Abbreviations: CCT = combined cortical thickness; FT_4I = free thyroxine index.

*Postmenopausal women only.

Age and Menopausal Status

Age proved to be the single factor most strongly related to CCT, with the mean CCT decreasing 0.045 mm per year. In part this decrease was accounted for by two other closely related variables: (1) the number of years since menopause was inversely related to CCT, and (2) the number of years taking estrogen-replacement therapy was directly related. A highly significant ($P<.001$) correlation was found between CCT and the difference of these two variables (that is, years beyond menopause without estrogen replacement).

Height and Weight

The CCT increased significantly with height; for a given height, however, the CCT increased only moderately with increasing weight. The Quetelet index (weight divided by height squared) was much less effective as a predictor of CCT than height and weight combined, or even height alone.

Thyroid Dosage and FT_4I

After adjustment for age, years beyond menopause without estrogen replacement, height and weight, the mean CCT of the users of 3 and 4 grains was 0.24 mm lower than that of the groups using 1 and 2 grains ($P<.01$). The FT_4I was also inversely related to CCT ($P<.01$), but this relation was not linear. Below 400, CCT and FT_4I were not related, but the CCT of women with FT_4I's greater than 400 was 0.27 mm below the mean.

Taken together, the factors of age, years beyond menopause without estrogen replacement, height, weight, thyroid dosage and FT_4I accounted for 51 percent of the total variance in CCT. Stepwise multiple regression analysis of these factors yielded regression coefficients that are summarized in

TABLE 2.—*Regression Analysis of Significant Independent Variables**

Variable	*Regression Coefficient (R^2)*	*Partial R^2*	*Student's t-Value*	*Level of Significance*
Age	−0.038 mm/yr	−0.461	6.2	$P<.0001$
Years postmenopausal without estrogen	−0.025 mm/yr	−0.285	3.6	$P<.001$
Height	+0.024 mm/cm	+0.260	3.0	$P<.001$
Thyroid dose				
3 grains	−0.240 mm	−0.162	1.9	$P<.02$
3 and 4 grains	−0.240 mm	−0.160	2.0	$P<.02$
Free thyroxine index (FT_4I)	−0.001 mm/FT_4I	−0.146	1.8	$P<.02$
Weight	+0.011 mm/kg	+0.177	2.2	$P<.01$

*Combined cortical thickness (CCT) is a dependent variable.

Table 2. The variance in CCT accounted for by age alone is reduced slightly when age is considered together with the other significant variables (0.045 mm per year to 0.038 mm per year). A 3-grain dosage of thyroid showed an identical regression coefficient to 4 grains, but the number of 4-grain users was too small to give statistical significance when examined alone. Therefore we pooled the 3- and 4-grain users in our analysis. Except for women aged 70 or older, an unexpected result was that CCT tended to increase with duration of thyroid use. After regression adjustment for the other variables, this increase was not significant ($P<.10$) and may have been due to chance.

Smoking

Smoking history was not a significant variable.

Discussion

Ample evidence indicates an increased rate of bone loss in patients suffering from thyrotoxicosis.[1-4] Restoration of bone loss may follow correction of this metabolic disorder.[3] Three or more grains of desiccated thyroid daily may produce a mild form of thyrotoxicosis, inasmuch as physiologic suppression of thyroid-stimulating hormone in hypothyroid subjects is achieved with the equivalent of 2 grains.[7]

Among our study subjects, 81 percent used desiccated thyroid. Disagreement exists regarding the relative potency of desiccated thyroid and levothyroxine. Several studies[8-11] and standard endocrine texts have stated that 1 grain of desiccated thyroid is equivalent to 100 μg of levothyroxine sodium. Sawin and co-workers[12] suggested that 1½ grains of desiccated thyroid was equivalent to 100 μg of levothyroxine. In our initial experimental design, we chose to use the 1 grain-per-100-μg equivalence. When we analyzed our data using a 1½-grain-per-100-μg equivalence, the derived regression coefficients were only slightly reduced and the recalculated t and P values were essentially unchanged.

Daniell[13] showed that women who used 2 or 3 grains of thyroid hormone had a lower bone mass value than postmenopausal women who did not take thyroid. We stratified our subjects by their replacement dosage and their FT_3I and included a 1-grain thyroid group. Our data show that use of 3 or 4 grains of thyroid is associated with a lower CCT than is found with usage of 1 or 2 grains. We were unable to show a linear correlation between CCT and FT_4I, but a pronounced decrease in CCT occurred in subjects with higher than normal FT_3I (>400).

Numerous studies have shown that estrogen replacement therapy prevents loss of bone mineral in postmenopausal women.[14-16] Our data agree, showing a highly significant relation between the loss of CCT and the number of years since menopause without estrogen replacement. Our regression equation predicts a loss of 0.38 mm (8.6 percent) of CCT per decade in women using estrogen and a loss of 0.63 mm (14.3 percent) of CCT per decade in postmenopausal women who do not use estrogen. The generally accepted rate of bone loss in untreated postmenopausal women is 10 percent per decade.[14-16]

In 97 women aged 60 to 69 years, Daniell[17] showed that smoking was associated with less bone mineral unless a woman's weight exceeded 10 percent of ideal. He also confirmed the presence of more bone mass in long-term estrogen users but found that smokers did not derive this benefit. He found that height was not related to bone mass and neither was weight except in those women whose weight exceeded 10 percent of ideal. Lindsay[18] reported that women who smoke have reduced skeletal mass but do not lose bone more rapidly as they age. We found that height was more strongly associated with CCT than weight and

were unable to show that smoking adversely affected the CCT of any subset of women.

Women who take the equivalent of 3 or more grains of desiccated thyroid a day should be advised that this therapy is associated with a higher incidence of osteopenia. FT_4I values exceeding 400 indicate a high likelihood of bone loss, but many women taking 3 grains and some taking 4 grains do not have an elevated FT_4I. We suspect that isolated T_3 thyrotoxicosis associated with desiccated thyroid hormone use[19] accounted for the osteopenia found in these patients.

We can derive from Table 2 the combined effects of short stature (10 cm below the mean), low weight (10.0 kg below the mean) and nonuse of estrogen replacement therapy for 20 postmenopausal years with a 3- or 4-grain dosage of thyroid supplements resulting in an FT_4I of 400. These factors combined result in a CCT 38 percent lower than in women who were not exposed to these risk factors.

REFERENCES

1. Fraser SA, Anderson JB, Smith DA, et al: Osteoporosis and fractures following thyrotoxicosis. Lancet 1971 May 15; 1:981-983

2. Ikkos DG, Katsichtis P, Ntalles K, et al: Osteoporosis in thyrotoxicosis. Lancet 1971 Nov 20; 2:1159

3. Bayley TA, Harrison JE, McNeill KG, et al: Effect of thyrotoxicosis and its treatment on bone mineral and muscle mass. J Clin Endocrinol Metab 1980 May; 50:916-922

4. Meema HE, Meema S: Comparison of microradioscopic and morphometric findings in the hand bones with densitometric findings in the proximal radius in thyrotoxicosis and in renal osteodystrophy. Invest Urol 1972 Mar-Apr; 7:88-96

5. Garn SM: The Earlier Gain and the Later Loss of Cortical Bone in Nutritional Perspective. Springfield, Ill., Charles C Thomas, 1970

6. dos Remedios LV, Weber PM, Feldman R, et al: Detecting unsuspected thyroid dysfunction by the free thyroxine index. Arch Intern Med 1980 Aug; 140:1045-1049

7. Virtama P, Helelä T: Radiographic measurements of cortical bone: Variations in a normal population between 1 and 90 years of age. Acta Radiol Suppl 1969; 293:7-35

8. Stock JM, Surks MI, Oppenheimer JH: Replacement dosage of L-thyroxine in hypothyroidism—A re-evaluation. N Engl J Med 1974 Mar 7; 290:529-533

9. McGavack TH, Reckendorf HK: Therapeutic activity of desiccated thyroid substance, sodium L-thyroxine and D,L-triiodothyronine: A comparative study. Am J Med 1956; 20:774-777

10. Lavietes PH, Epstein FH: Thyroid therapy of myxedema: A comparison of various agents with a note on the composition of thyroid secretion in man. Ann Intern Med 1964 Jan; 60:79-87

11. Rees-Jones RW, Larsen PR: Triiodothyronine and thyroxine content of desiccated thyroid tablets. Metabolism 1977 Nov; 26: 1213-1218

12. Sawin CT, Hershman JM, Fernandez-Garcia R, et al: A comparison of thyroxine and desiccated thyroid in patients with primary hypothyroidism. Metabolism 1978 Oct; 27:1518-1525

13. Daniell HW: Replacement treatment of hypothyroidism (Letter). N Engl J Med 1974 Jul 11; 291:102

14. Meema S, Bunker ML, Meema HE: Preventive effect of estrogen on postmenopausal bone loss: A follow-up study. Arch Intern Med 1975 Nov; 135:1436-1440

15. Nordin BEC, Duursma SA: Estrogens and bones, chapter 11, *In* Keep V (Ed): Consensus of Menopausal Research. Baltimore, University Park Press, 1977

16. Lindsay R, Hart DM, Forrest C, et al: Prevention of spinal osteoporosis in oophorectomised women. Lancet 1980 Nov 29; 2:1151-1153

17. Daniell HW: Osteoporosis of the slender smoker: Vertebral compression fractures and loss of metacarpal cortex in relation to postmenopausal cigarette smoking and lack of obesity. Arch Intern Med 1976 Mar; 136:298-304

18. Lindsay R: The influence of cigarette smoking on bone mass and bone loss, *In* DeLuca HF (Ed): Osteoporosis: Recent Advances in Pathogenesis and Treatment. Proceedings of the Tenth Steenbock Symposium, Held at the University of Wisconsin-Madison, June 9-12, 1980. Baltimore, University Park Press, 1981

19. Dolman LI, Housel GJ, Lull RL: T_3 "toxicosis"—Significance in a large thyroid clinic population. Program and Abstracts of the 62nd Annual Meeting of the Endocrine Society, Abstract 457. Washington, DC, June 19, 1980

Refer to: Fletcher EC, Levin DC: Flexible fiberoptic bronchoscopy and fluoroscopically guided transbronchial biopsy in the management of solitary pulmonary nodules. West J Med 1982 Jun; 136:477-483

Flexible Fiberoptic Bronchoscopy and Fluoroscopically Guided Transbronchial Biopsy in the Management of Solitary Pulmonary Nodules

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In our experience with fluoroscopically guided flexible fiberoptic bronchoscopy (FFB), transbronchial biopsy, bronchial brush, bronchial washing (BW) and sputum cytology (SC) in 101 patients with solitary pulmonary nodules (SPN) less than 6 cm in diameter (without endobronchial tumor), a specific diagnosis was reached via FFB in 36 cases. The diagnostic yields in primary lung malignant lesions (PLM), metastatic lesions and benign SPN were 58 percent, 28 percent and 10 percent, respectively. Size affected diagnostic efficiency considerably, with a 12 percent yield in lesions under 2 cm, a 40 percent yield in lesions 2 to 4 cm and a 63 percent yield in lesions over 4 cm. BW and SC (prebronchoscopic) did not contribute enough information to justify their cost. FFB directly affected therapy in 17 patients who were not thoracotomy candidates and may have influenced the decision for surgical treatment in another 19 patients diagnosed as having PLM. In 65 patients results of FFB were negative and the procedure did not appear to directly affect subsequent management because malignancy was not ruled out.

ESTABLISHING THE CAUSE of the solitary pulmonary nodule (SPN) remains a problem to clinicians. Numerous articles have attempted to establish guidelines for systematic handling of the SPN. Some authors[1-3] advocate an organized approach using various clinical criteria (that is, age, growth rate, roentgenographic appearance) and nonsurgical diagnostic means (sputum cytology, nuclear scans, bronchial brush cytology, needle aspiration) to distinguish benign from malignant lesions. Other authors[4] caution that these procedures not only lead to delay in the treatment of potentially curable malignant lesions but add considerable morbidity, discomfort and hospital cost and, in some circumstances, may disseminate tumor cells.

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Submitted, revised, September 21, 1981.

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ABBREVIATIONS USED IN TEXT

BB = bronchial brush
BW = bronchial washing
COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in one second
FFB = flexible fiberoptic bronchoscopy
FVC = forced vital capacity
PLM = primary lung malignancy
SC = sputum cytology
SPN = solitary pulmonary nodule
TBB = transbronchial biopsy

Whether or not these studies produce positive or negative findings, thoracotomy is still indicated unless a specific benign process is found.[5]

The applicability of these diagnostic techniques to the SPN appears to depend on their accuracy and relative safety. Numerous articles[3,6-8] address these two aspects of the nonsurgical diagnostic tools. In the final analysis the usefulness of any diagnostic technique is determined by its therapeutic implications to patients.

Fluoroscopically guided flexible fiberoptic bronchoscopy (FFB) in conjunction with transbronchial biopsy (TBB), bronchial brush (BB) or bronchial washing (BW) cytology has given physicians an additional procedure for nonsurgical diagnosis of the SPN. Several articles[9-15] have presented data on the diagnostic accuracy of these methods but none have addressed the ultimate effect of FFB on patient care and the cost to this group of patients.

We report the diagnostic accuracy of FFB in 101 consecutive cases of SPN evaluated at the University of Oklahoma Health Sciences Center and the Veterans Administration Medical Center in Oklahoma City from April 1, 1978, to December 31, 1979. In addition, we have assessed the effect of TBB, BB and BW on therapy and hospital cost in these patients.

Methods

We reviewed the records and roentgenograms of 103 patients bronchoscoped to establish the cause of their SPN. Two patients with SPN and endobronchial malignancy were excluded from this series because we wished to examine the yield of "blind" (nondirect visualization) bronchoscopic procedures. Of the remaining 101 patients, 92 were men and 9 were women. The mean age of the group was 60 years (range 29 to 89 years). A total of 88 were smokers with a mean pack-year history of 58. The radiographic criteria used for SPN were those of Steele[16] and patients with symptoms were also included in our study. All lesions were 6 cm or less in diameter.

Of 92 patients in whom spirometry was done, 66 had evidence of airways obstruction based on a greater than 20 percent reduction in forced expiratory volume in one second (FEV_1) and an FEV_1 versus forced vital capacity (FVC) of 70 percent or less. The mean FEV_1 for the obstructed group was 1.88 liters (range 0.62 to 3.88 liters), while the mean FEV_1 for the entire group tested was 3.18 liters. Four patients in whom spirometry was not done were diagnosed as having chronic obstructive pulmonary disease (COPD) based on clinical history and roentgenographic findings. Twenty-three patients had symptoms attributable to the SPN (weight loss, hemoptysis, chest pain) and 12 had previously resected primary tumors (six had lung tumors, four had tumors of the head and neck and two had tumors of the colon).

The technique for FFB, TBB and cytology collection has been previously described in detail.[9,17] The bronchoscope (Olympus BF-B2) was introduced transnasally after local anesthesia had been achieved with lidocaine. Fluoroscopically guided TBB was carried out in 118 of the 120 bronchoscopies done. TBB was prevented in two cases because of lack of fluoroscopic visualization and bronchospasm. A variety of cytologic specimens (including sputum, bronchial brush and bronchial wash with 60 ml of normal saline) were collected in all cases. All cytology specimens were handled in the routine cytopathology laboratory and final interpretation was made by one cytopathologist.

A histologic diagnosis of nonspecific fibrosis or chronic inflammation was considered to be nondiagnostic even when the final diagnosis proved to be a benign process. These nonspecific entities are often found in TBB taken near malignant disease and do not alter the course of the diagnostic workup.[18] Anatomic location of the SPN was determined using standard anteroposterior and lateral chest roentgenograms, tomograms when available, and fluoroscopy at bronchoscopy and surgical procedure when these were carried out. A modified scheme of ten anatomic segments was used to classify the SPN location: right and left upper lobe anterior segments, right and left upper lobe apical-posterior segments, right middle lobe, lingula, right and left lower lobe superior segments and right and left lower lobe basilar segments (Figure 1).

Size and anatomic location of the SPNs were compared with success at establishing a specific diagnosis by FFB using one-way analysis of variance. SPN size by group (up to 1.9 cm, 2 to 4 cm, 4.1 to 6.0 cm), radiographic shape, margin characteristics and anatomic location were compared with success at establishing a bronchoscopic diagnosis using chi-square analysis.

Results

A definite diagnosis was ultimately established in 89 of 101 patients (Table 1). In 36 cases a diagnosis was established by bronchoscopy and in 32 by a major surgical procedure (mediastinoscopy, left second interspace exploration or thoracotomy). The final diagnosis in 16 patients was established on clinical grounds—five by findings of mycobacteria on sputum cultures and radiographic response to antituberculous drugs, eight by resolution roentgenographically of the SPN without specific therapy and three by the subsequent appearance of new pulmonary nodules and discovery of a primary carcinoma. In five patients a definite diagnosis was established by other means —two by rib biopsy under local anesthesia, one by needle biopsy, one by subsequent endobronchial biopsy following tumor spread and one by pulmonary artery angiography showing an arterial aneurysm.

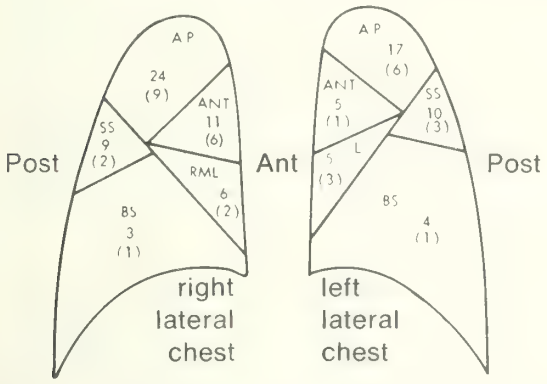

Figure 1.—Schematic representation of lateral view of both lungs (Post = posterior; Ant = anterior) showing the anatomic location (top number) and the number of nodules diagnosed by flexible fiberoptic bronchoscopy in that segment (number in parentheses). AP = apical posterior segment, upper lobe; ANT = anterior segment, upper lobe; L = lingula; RML = right middle lobe; SS = superior segment of lower lobe; BS = basilar segments of lower lobe.

FFB gave specific tissue or cytologic diagnosis in 36 cases (Table 1). Bronchoscopy provided correct identification in 31 of 53 proved primary lung malignant lesions (Table 2) but only two of seven metastatic nodules. Thus, the sensitivity (true-positives versus true-positives plus false-negatives) for bronchoscopy in diagnosing malignant SPN was 55 percent. The specificity (true-negatives versus true-negatives plus false-positives) was 100 percent for malignant lesions because no false-positives were found in this study. Of 29 nonmalignant SPNs, 20 had a definite diagnosis established by sputum culture or histology. Only 3 of these 20 were confirmed by FFB, a sensitivity of 15 percent. Again, there were no false-positives, giving a specificity of 100 percent.

Specific diagnosis was determined more often

TABLE 1.—*Methods of Establishing a Definite Diagnosis*

	Bronchoscopy		*Surgical Procedure*			
	*TBB**	*Cytology†*		*Clinical*	*Other*	*Total*
Primary lung carcinoma						
Squamous cell	14	3	6	..	2	25
Adenocarcinoma	8	1	5	..	..	14
Large cell	2	..	6	..	1	9
Oat cell	1	..	1	..	..	2
Alveolar cell	2	..	1	..	..	3
Metastatic lesion	2	..	1	3	1	7
Tuberculoma	1	..	3	5	..	9
Benign infiltrate	..	..	..	8	..	8
Fungal disease	..	..	4	..	..	4
Lung abscess	2	..	1	..	..	3
Pulmonary dirofilariasis	..	..	1	..	..	1
Pulmonary artery aneurysm	..	..	..	..	1	1
Amyloidosis	..	..	1	..	..	1
Lymphomatoid granulomatosis	..	..	1	..	..	1
Necrotizing granuloma, no apparent cause	..	..	1	..	..	1
TOTALS	32	4	32	16	5	89

*Transbronchial biopsy.
†Including brush, wash and postbronchoscopy sputum.

by TBB than by cytology. Of the 36 correctly identified lesions 32 were diagnosed from the TBB tissue. A total of 511 specimens for cytology (an average of 5.05 per patient) collected by the various methods yielded a specific diagnosis in only 25 cases (bronchial brush 18, bronchial wash 2, prebronchoscopy sputum 1, postbronchoscopy sputum 4) (Table 3). In four cases where cytology was the only diagnostic source, bronchial brushing yielded the necessary tissue in two cases and postbronchoscopy sputum in the other two.

Nineteen patients were bronchoscoped a second time when the first procedure failed to yield a specific diagnosis. Six of these repeat bronchoscopies provided a diagnosis, five by TBB and one by cytology (BB) (Table 2). All three benign lesions in which FFB was successful were diagnosed on the second bronchoscopy.

There was a positive correlation ($P<.0001$) between radiographic size of the SPN and establishment of a specific diagnosis by FFB. The mean size of successfully diagnosed lesions was 3.55 cm while undiagnosed lesions averaged 2.45 cm (Table 4). Chi-square analysis showed no evidence that anatomic location (Figure 1), radiographic shape or character of the margin affected the success rate of FFB.

At the termination of this study a final diagnosis had not been established in 12 patients. Of these 12, 3 had radiographically stable lesions after 12, 18 and 22 months, respectively. Subsequent films showed enlargement in three cases suspected of being malignant. Four patients proved to have malignant primary lesions and the SPNs were believed to be slow-growing metastasis. Two patients were lost to follow-up immediately after discharge and had no subsequent roentgenograms.

In a total of 120 bronchoscopies that were carried out, ten patients had complications associated with the procedure. Five had pneumothoraces (three of these required closed chest tube drainage), one had severe bronchospasm and four had apparent substantial bleeding (lobar infiltrate or persistent hemoptysis). Bleeding resolved in all four of these patients within 48 hours and no transfusions were required.

TABLE 2.—*Diagnostic Accuracy of Bronchoscopy*

Final Diagnosis	*Number of Procedures*	*Successful on First Bronchoscopy*	*Successful on Second Bronchoscopy*	*Total Yield (percent)*
Bronchogenic carcinoma	53	28	3	58.5
Metastatic tumor	7	2		28.5
Benign disease	29	0	3	10.3
TOTAL	89			

TABLE 3.—*Yield of Sampling Method in Bronchoscopy**

Method	*Number of Procedures*	*Positive Yield (percent)*
Transbronchial biopsy	118	27.0
Bronchial brush	116	15.5
Bronchial wash	54	4.0
Sputum cytology		
Prebronchoscopy	179	0.5
Postbronchoscopy	162	2.4

*120 bronchoscopies in 101 patients. Suspicious cytologies were considered negative.

TABLE 4.—*Bronchoscopic Yield by Nodule Size*

Size cm	*Number of Procedures*	*Diagnosed*	*Yield (percent)*
<2	32	4	12.5
2-4	50	20	40.0
>4	19	12	63.1

Discussion

This study considers SPNs in predominantly older male smokers. Previously published data[1,2,16] suggest that a large proportion of these would be malignant. In our study, all malignant nodules were found in patients aged 45 years and over. Because of the high incidence of malignancy in this group, there was a significant probability that a major surgical procedure would be needed whether or not the diagnosis was made beforehand by FFB. The only way bronchoscopy could prevent thoracotomy in operative candidates was to show a benign lesion, endobronchial disease, vocal cord paralysis or widening of the carina, which would preclude curative resection.

We examined several factors that might have predicted benignity of the SPN. The presence or absence of symptoms was not helpful in that 12 patients with benign lesions were symptomatic, as were eight patients with malignant nodules. The absence of a smoking history was not predictive; four of the nine nonsmokers had primary lung tumors (two had adenocarcinoma, one had squamous cell and one had alveolar cell). Although larger sizes correlated significantly with malignancy, it was of no benefit in predicting individual cases as 9 of 32 lesions smaller than 2 cm were malignant.

Our overall diagnostic yield with FFB was 35.6 percent. This result is lower than that of other published series (Table 5) because of the unse-

TABLE 5.—*Published Results of Flexible Fiberoptic Bronchoscopy With Transbronchial Biopsy in Evaluating Solitary Pulmonary Nodules (SPN's)*

	Number of Patients	*Overall Diagnostic Yield percent*	*Number of Patients*	*Diagnostic Yield in Primary Lung Neoplasm (percent)*
Ellis[9]	65	75	44	67
Stringfield et al.[10]*	27	48	27	48
Hanson et al.[11]	56	53		
Schoenbaum et al.[12]	18	77	10	80
Radke et al.[13]	97	56	62	66
Zavala[14]*	169	64	120	70
Mark et al.[15]	60	31	32	53
Present study	101	36	53	58

*Malignant SPN's only, others include benign lesions.

lected nature of the cases and the requirement of specific findings on histology to be considered diagnostic. The overall yield in one of the studies[9] drops from 75 percent to 55 percent if histologic findings termed "acute and chronic inflammation" are not considered diagnostic. Because both inflammation and fibrosis may be found in association with malignant processes, this finding in TBB tissue does not rule out malignancy. Of 26 patients in our study whose TBB recovered tissue showing nonspecific fibrosis and inflammation, ten patients eventually proved to have a malignant nodule. Thoracotomy, needle biopsy or roentgenographic follow-up is still necessary to confirm or refute benignity. If only nodules that require specific histologic findings (such as primary lung malignancy) are considered, our diagnostic yield of 58 percent compares favorably with the yield in other studies (Table 5).

In some cases, bronchial brush and sputum cytology (postbronchoscopy) complemented the results from TBB by providing the diagnosis. Specimens from BB showed definite malignancy in 18 of 116 specimens but BB was necessary for the diagnosis in only two cases where results of both TBB and BW were negative. Bronchial washing was diagnostic in 2 of 54 specimens but TBB also gave positive findings in both cases. Cytology of sputum collected before bronchoscopy added nothing to the information obtained by TBB. Postbronchoscopy sputum cytology had a low yield (2.4 percent) but did give a diagnosis in two cases where the findings on TBB were negative.

The total cost of the 511 cytology specimens in this study was $8,176. Of the four methods of collection, BB had the highest positive yield (15.5 percent) per number of specimens. Its yield-cost ratio was 0.68. Sputum cytology (postbronchoscopy) had a yield-cost ratio of 0.07 but was necessary for diagnosis in two cases. This low yield-cost ratio may have been due to the large number of specimens collected (162). In general, if the first postbronchoscopy sputum was positive, so were subsequent specimens. BW and prebronchoscopy SC added nothing to information collected by other means, yet accounted for 45 percent of the cost of cytology. These data suggest that BW and SC were not cost effective. Kvale and co-workers[19] reached a similar conclusion. Postbronchoscopy sputum cytology may be useful but should probably be limited to one specimen.

Because of the clinical suspicion of a benign SPN or because of a high operative risk, we repeated bronchoscopy in 19 patients. Six of these attempts were diagnostic (31 percent) and three of the six showed benign disease (two showed lung abscesses and one tuberculosis). Eleven of the 19 patients proved to have a malignancy and 9 of these had thoracotomy. The indications and results of second attempts at FFB are not discussed in the literature. We felt that a second attempt was indicated if the SPN was strongly suspected of being benign (for example, when a patient was a nonsmoker) or when a patient was at a high surgical risk and a diagnosis was needed to initiate chemotherapy or radiation therapy. At other centers an alternative nonsurgical procedure after the first attempt at TBB failed would have been transthoracic needle aspiration.[15,20]

It is important to consider what effect FFB had on patient management and to evaluate the diagnostic yield and clinical usefulness of this procedure (Figure 2). Of 101 patients with an SPN, FFB did not give a precise diagnosis in 65. Since negative results from TBB and BB do not exclude malignancy from the differential diagnosis, the decision to excise, treat nonsurgically or follow clinically could not be made on the basis of bronchoscopic results. Thoracotomy was required for diagnosis of the nodule in 32 patients while 33 were not operated on for various reasons that included underlying lung disease, poor general health, clinical suspicion of a metastatic nodule or refusal of thoracotomy by a patient. Of the latter 33 patients, 21 had final diagnoses made by nonbronchoscopic, nonsurgical methods and appropriate therapy was instituted. It could be argued that in these 65 patients, bronchoscopy was useful in ruling out endobronchial disease.

Although this aspect of FFB is important to the thoracic surgeon, it could be accomplished at a lower risk and cost to the patient by a simple bronchoscopic examination (open tube or FFB) without TBB immediately before thoracotomy.

Of 36 patients in whom a definite diagnosis was made by flexible fiberoptic bronchoscopy, 17 benefited directly from the procedure by receiving antibiotic medication or radiation therapy or by the establishment of a diagnosis even though therapy was refused. Nineteen patients had thoracotomies from which histologic diagnosis of a malignant SPN was confirmed. In this group, knowledge gained from bronchoscopy that a malignant nodule was present may have influenced the decision to operate. It also may have altered the surgical approach by eliminating the need for a wedge resection or frozen section before lobectomy. At the same time all 19 patients would have been strongly considered for resection (based on age, sex, smoking history, radiographic findings and adequate pulmonary function tests) had bronchoscopy been negative or not been done. In these cases, bronchoscopy may have been an additional, unnecessary procedure. We could not answer this question based on data from this study.

We examined data to see if bronchoscopy influenced the decision to operate on SPNs in 21 high surgical risk patients with underlying lung disease as determined by spirometry (FEV_1 of 1.3 to 1.8 liters).[21] In this group, four out of a total of eight patients with nodules diagnosed as malignant by FFB later underwent resection. Of 13 similar patients in whom bronchoscopy was unsuccessful, 7 had exploratory thoracotomies. Thus, factors other than diagnosis by bronchoscopy appeared to influence the decision to operate, to follow clinically or to treat medically.

We concluded that FFB with TBB and various cytologic methods played a major role in therapeutic decisions in 17 of the 101 SPN patients bronchoscoped. It may have been of value in an additional 19 percent or been an unnecessary procedure. It did not influence therapy in 64 percent of our patients based on lack of diagnostic tissue recovered.

A conservative estimate of the cost of fiberoptic bronchoscopy at our institution is $550 per patient per procedure, which includes a one-day stay in hospital, laboratory tests before the procedure, pathology and cytology fees, fluoroscopy time and bronchoscopist's fee. The total estimated cost of the 120 bronchoscopies was $66,000; this estimate does not take into consideration hospital stays longer than one day or cost of chest tubes and so forth. However, bronchoscopy obviated the need for 13 diagnostic thoracotomies, which saved

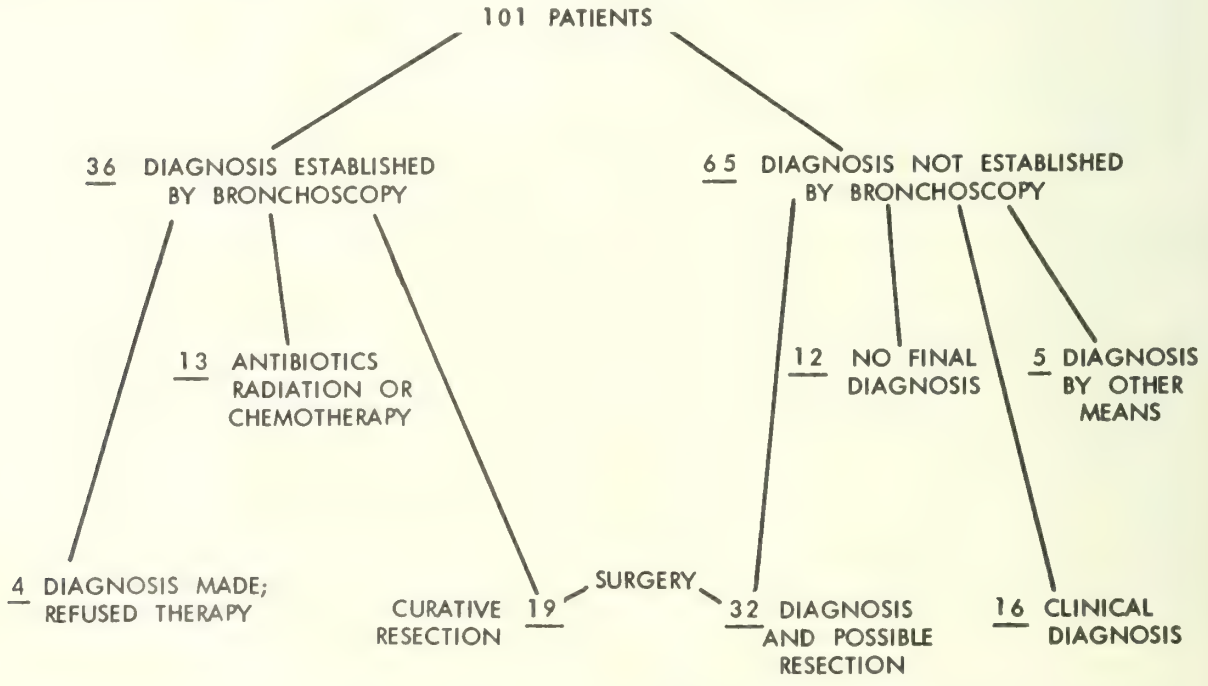
101 PATIENTS
36 DIAGNOSIS ESTABLISHED BY BRONCHOSCOPY
65 DIAGNOSIS NOT ESTABLISHED BY BRONCHOSCOPY
13 ANTIBIOTICS RADIATION OR CHEMOTHERAPY
12 NO FINAL DIAGNOSIS
5 DIAGNOSIS BY OTHER MEANS
4 DIAGNOSIS MADE; REFUSED THERAPY
CURATIVE RESECTION 19
SURGERY
32 DIAGNOSIS AND POSSIBLE RESECTION
16 CLINICAL DIAGNOSIS

Figure 2.—Diagram showing the effect of flexible fiberoptic bronchoscopy on patient management. See text for details.

considerable cost and substantial patient morbidity. Although expensive, we are left with a useful diagnostic procedure that may have a definite effect on the management of a third of patients with SPN.

Clearly, the answer to this dilemma lies in selecting which patient with an SPN should be bronchoscoped and which should have thoracotomy. The broad application of FFB and TBB with cytology to this population (predominantly male smokers over age 45) may not be justified on a cost-effective basis, as benign lesions have a low diagnostic yield and malignant lesions often are removed surgically because they are frequently the most resectable form of lung cancer. In this particular population of patients with SPNs, data suggest a relative benefit from FFB for the following patients: (1) those in whom lung resection has been ruled out but a tissue diagnosis is needed for radiation or chemotherapy, (2) those in whom lung metastasis is suspected, (3) those who refuse thoracotomy unless a definite diagnosis of cancer is made and (4) those whose lesions are over 2 cm in diameter.

In our review of these cases we found at least four examples where follow-up chest roentgenograms taken two to four weeks after bronchoscopy showed partial or complete resolution of the solitary nodule. These nodules were usually very small (less than 0.5 cm) and had nondiscrete borders. It is conceivable that withholding bronchoscopy two to four weeks when these small "soft" nodules are discovered would allow time for small localized infectious processes to resolve. Also, sputum cultures for acid-fast bacilli should be available and reported as negative before bronchoscopy or before a surgical procedure in patients with a past history of tuberculosis or predisposing factors to the development of tuberculosis.

The data further suggest that bronchial washing and sputum for cytology add little to the information obtained by TBB and bronchial brush and therefore these procedures are not cost effective.

REFERENCES

1. Lillington GA: The solitary pulmonary nodule—1974. Am Rev Respir Dis 1974 Dec; 110(6):669-707

2. Nathan MH: Management of solitary pulmonary nodules. JAMA 1974; 227:1141-1144

3. Sinner WN: Transthoracic needle biopsy of small peripheral malignant lung lesions. Invest Radiol 1973; 8:305-314

4. Ray JF, Lawton BR, Magnin GE, et al: The coin lesion story: Update 1976. Chest 1976; 70:332-336

5. Moser KM: Solitary pulmonary nodules (Editorial). JAMA 1974; 227:1167-1168

6. Zavala DC, Richardson RH, Mukerjee PK, et al: Use of the bronchofiberscope for bronchial brush biopsy—Diagnostic results and comparison with other brushing techniques. Chest 1973 Jun; 63:889-892

7. Zelch JV, Lalli AF, McCormack LJ, et al: Aspiration biopsy in diagnosis of pulmonary nodule. Chest 1973; 63:149-152

8. Jamplis RW, Stevens GM, Lillington GA: Percutaneous needle aspiration biopsy of lung. Am J Surg 1968; 116:243-250

9. Ellis JH: Transbronchial lung biopsy via the fiberoptic bronchoscope. Chest 1975; 68:524-532

10. Stringfield JT, Markowitz DJ, Bentz RR, et al: The effect of tumor size and location on diagnosis by fiberoptic bronchoscopy. Chest 1977 Oct; 72:474-476

11. Hanson RR, Zavala DC, Rhodes ML, et al: Transbronchial biopsy via flexible fiberoptic bronchoscope: Results in 164 patients. Am Rev Respir Dis 1976; 114:67-72

12. Schoenbaum SW, Koerner SK, Ramakrishna B, et al: Transbronchial biopsy of peripheral lesions with fluoroscopic guidance: Use of the fiberoptic bronchoscope. J Can Assoc Radiol 1974 Mar; 25:39-43

13. Radke JR, Conway WA, Eyler WR, et al: Diagnostic accuracy in peripheral lung lesions—Factors predicting success with flexible fiberoptic bronchoscopy. Chest 1979 Aug; 76(2):176-179

14. Zavala DC: Diagnostic fiberoptic bronchoscopy: Techniques and results of biopsy in 600 patients. Chest 1975 Jul; 68(1):12-19

15. Mark JBD, Marglin SI, Castellino RA: The role of bronchoscopy and needle aspiration in the diagnosis of peripheral lung masses. J Thorac Cardiovasc Surg 1978; 76:266-268

16. Steele LT: The Solitary Pulmonary Nodule. Springfield, Charles C Thomas, 1964, p 4

17. Levin DC, Wicks AB, Ellis JH Jr: Transbronchial biopsy via the fiberoptic bronchoscope. Am Rev Respir Dis 1974; 110:4-12

18. Wilson RK, Fechner RE, Greenberg SD, et al: Clinical implications of a nonspecific transbronchial biopsy. Am J Med 1978 Aug; 65(2):252-256

19. Kvale PA, Bode FR, Kini S: Diagnostic accuracy in lung cancer; comparison of techniques used in association with flexible fiberoptic bronchoscopy. Chest 1976 Jun; 69:752-757

20. Borgeskov S, Francis D: A comparison between fine-needle biopsy and fiberoptic bronchoscopy in patients with lung lesions. Thorax 1974 May; 29:352-354

21. Boushy SF, Billig DM, North LB, et al: Clinical course related to preoperative and postoperative pulmonary function in patients with bronchogenic carcinoma. Chest 1971; 59:383-391

Refer to: White TT: Obstructive biliary tract disease (Medical Progress). West J Med 1982 Jun; 136:484-504

Obstructive Biliary Tract Disease

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The techniques that have come into general use for diagnosing problems of obstructive jaundice, particularly in the past ten years, have been ultrasonography, computerized tomography, radionuclide imaging, transhepatic percutaneous cholangiography using a long thin needle, transhepatic percutaneous drainage for obstructive jaundice due to malignancy, endoscopic retrograde cannulation of the papilla (ERCP), endoscopic sphincterotomy and choledochoscopy. It is helpful to review obstructive jaundice due to gallstones from a clinical point of view and the use of the directable stone basket for the retrieval of retained stones, choledochoscopy for the same purpose using the rigid versus flexible choledochoscopes and dissolution of stones using various fluids through a T tube.

The use of dilation of the sphincter for the treatment of stenosis or stricture of the bile duct is now frowned on; rather, treatment choices are between the use of sphincteroplasty versus choledochoduodenostomy and choledochojejunostomy. Any patient with obstructive jaundice or anyone undergoing manipulation of the bile ducts should have prophylactic antibiotic therapy.

The current literature regarding treatment of cancer of the bile ducts is principally devoted to the new ideas relative to treatment of tumors of the upper third, especially the bifurcation tumors that are now being resected rather than bypassed. Tumors of the distal bile duct are still being resected by focal operations. Finally, it is now felt that early operation for congenital biliary atresia and choledochal cysts gives the best prognosis, with preoperative diagnosis now possible with the use of ultrasonography and ERCP.

THE CAUSES of extrahepatic obstruction to the bile duct include gallstones in the extrahepatic ductal system, tumors of the bile ducts and pancreas, bile duct atresia and stricture, choledochal cysts and parasites such as *Clonorchis sinesis* and *Ascaris lumbricoides*. Because jaundice due to bile duct obstruction in no way differs from that of intrahepatic cholestasis, we will begin with a very brief discussion of the traditional methods of differentiating a diagnosis of obstructive from other types of jaundice by clinical laboratory analyses that are still in use.

Obstructive jaundice begins insidiously and

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ABBREVIATIONS USED IN TEXT

ACMI = American Cystoscope Makers, Inc.
CT = computerized tomography
ERCP = endoscopic retrograde cholangiopancreatography
GOT = glutamic-oxaloacetic transaminase (now aspartate aminotransferase)
GPT = glutamic-pyruvic transaminase (now alanine aminotransferase
HIDA = USAN code designation for *N*-substituted iminodiacetic acid (Lidofenin)
PTC = percutaneous transhepatic cholangiography

steadily worsens without preliminary gastrointestinal disturbances. Patients with gallstones may have had previous attacks of colic or even an episode of jaundice with the passage of a stone. Some patients with calculi may have painless jaundice. Most patients with carcinoma of the pancreas have back and epigastric pain. Cancer of the pancreas is usually preceded by pain and loss of weight and at times accompanied by steatorrhea.

Other possible diagnoses are ampullary or bile duct carcinomas. About a million new cases of cholelithiasis are discovered in the United States each year, of which about 80,000 (8 percent) have common bile duct stones. There are about 25,000 new cases of carinoma of the pancreas each year, about half of which are accompanied by jaundice, and 7,000 to 8,000 new cases of bile duct tumors. We are recognizing increasing numbers of new cases of jaundice due to parasitic infestation of the bile ducts in Asian refugees to the United States. We are also seeing strictures of the bile duct due to surgical injury at the rate of 1 or 2 per 1,000 operations on the extrahepatic biliary system.[1-3]

The liver swells considerably when the main bile ducts are obstructed, with the result that this enlargement of the liver strongly suggests mechanical obstruction rather than hepatitis or drug-induced jaundice. A palpably enlarged gallbladder suggests malignant extrahepatic obstruction rather than gallstones.

Physiologic Tests

Jaundice due to conjugated bilirubin is accompanied by bilirubinuria. This is due to reflux of conjugated bilirubin into the circulation usually due to obstruction of the bile ducts that, when complete, is accompanied by white stools devoid of bilirubin metabolites and characterized by the disappearance of urobilin from the urine. Reflux can also be caused by lesions of the liver cells due to hepatitis or cirrhosis. Liver cells continue to conjugate the bilirubin, but the excretion of conjugated bilirubin in the bile is diminished.

Serum alkaline phosphatases hydrolyze phosphoric acid esters in an alkaline medium. The levels of serum alkaline phosphatase are expressed in conventional units: their normal concentration is between 1.5 and 4 Bodansky units (BU), 3 to 15 King-Armstrong units or 20 to 85 IU per dl. The serum alkaline phosphatase levels are elevated in obstructive jaundice and infiltrative lesions of the liver. The mechanism of this increase is thought to be an increased production of phosphatases by the liver cells. One sees a moderate elevation of serum alkaline phosphatase in the course of cirrhosis or acute hepatitis. An elevated alkaline phosphatase level is not specific for liver diseases as it also occurs in association with lesions of the bones. The concentrations of the other two serum enzymes, 5-nucleotidase and leucine aminopeptidase, parallel that of the alkaline phosphatases in liver disease but their concentrations do not increase in bone disease. The isoenzymes of phosphatase can be easily identified by electrophoresis if there is doubt as to their origin.

The liver synthesizes and esterifies most cholesterol but some esterification also takes place in the plasma. The latter esterification depends on the lecithin-cholesterol-acyltransferase synthesized by the hepatocyte and released into the circulation. The serum concentration of cholesterol usually is between 180 and 250 mg per dl, with 40 percent unesterified and 60 percent esterified. The level of serum cholesterol rises in cases of obstructive jaundice because, as with the serum alkaline phosphatases, the hepatocyte produces increased quantities of this material. An elevated serum cholesterol level is not found in all cases of obstructive jaundice, and it may be elevated in some cases due to effects of drugs. The proportion of esterified cholesterol diminishes in liver failure.

Transaminases catalyze the transfer of amine groups to ketoacids. Glutamic-pyruvic transaminase (GPT), or alanine aminotransferase, and glutamic-oxaloacetic transaminase (GOT), or aspartate aminotransferase, are present in the serum. The normal values vary from laboratory to laboratory depending on method. These enzymes are present in an abundance in body tissues. The liver contains more GPT than GOT but the muscles, particularly those of the heart, contain more GOT.

The transaminases pass in large quantities into the serum in liver necrosis. Serum GPT levels are initially more elevated than GOT. The plasma levels of GOT later will be higher than those of GPT because of the prolonged survival of GOT.[1-5]

Thus, in cholestasis there is an elevation of serum concentration of conjugated bilirubin, cholesterol and alkaline phosphatase. The prothrombin time is prolonged due to reduced absorption of vitamin K, but becomes normal after parenteral administration of this vitamin.

Imaging Techniques

The simplest imaging technique for diagnosing obstructive jaundice is that of taking a plain x-ray film of the abdomen. This technique is very useful diagnostically when stones can be seen but, unfortunately, only 10 percent to 15 percent of gallstones contain enough calcium to be radiopaque. This approach is also valuable in the unusual instance where gas can be seen in the gallbladder or calcium appears in the wall of the gallbladder. A plain abdominal film should be made before any other type of study.[6]

Ultrasonography

Diagnostic ultrasonography uses sound waves that are reflected from interfaces between tissues, which produces differences in acoustic impedance. At first these instruments were capable of producing only black and white images but now can produce images with eight or more shades of grey (B mode) so that a much clearer picture of anatomic and pathologic structures can be obtained. This approach can show sonolucent bile in the gallbladder lumen and a collection of echoes in the dependent portion of the gallbladder produced by the stones, with acoustic shadows posterior to each calculus. Using ultrasonography it is possible to detect more dilated bile ducts and thus we can determine whether we are dealing with obstructive or hepatocellular jaundice. Dilatation of the extrahepatic bile ducts tends to occur in obstructive jaundice before any changes occur in the intrahepatic ducts and can be presented even before abnormalities are seen in liver function tests. A normal-sized common hepatic duct and the proximal portion of the common bile duct can be detected in oblique views anterior to the portal vein in most patients. The distal portion of the common bile duct can be seen less often. Stones are usually not seen in the enlarged distal common bile duct. Enlargement of the head of the pancreas can be detected, but it is impossible to use this technique to differentiate between cancer and pancreatitis.[7-13] It must be remembered that normal-sized ducts may be obstructed and dilated ducts may be unobstructed (Figures 1 and 2).

Computed Tomography

Computerized tomography (CT) is an x-ray technique wherein differences in tissue density can be identified with the use of a computer. The

Figure 1.—Ultrasonography image showing the dilated common bile duct **(arrow)** adjacent to the portal vein in a patient with carcinoma of the distal bile duct.

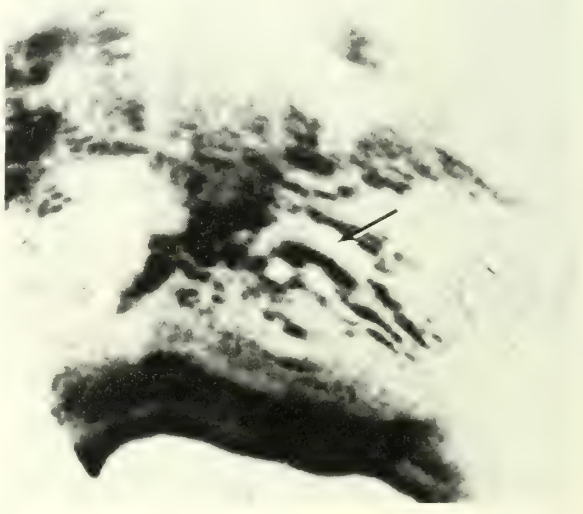

Figure 2.—Ultrasonography image showing the dilated common bile duct adjacent to the portal vein **(arrow)** in the same patient as Figure 1, but from another angle.

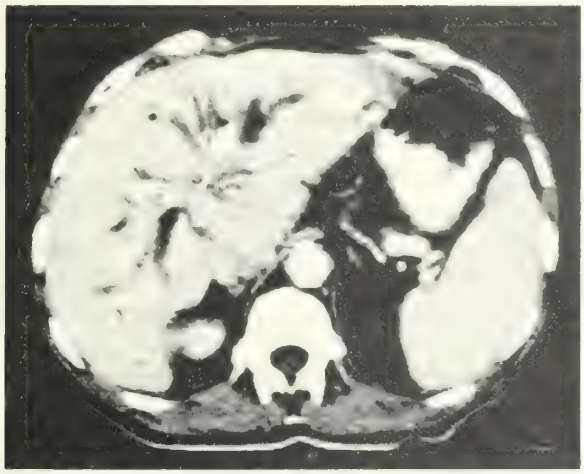

Figure 3.—CT scan image showing dilated hepatic ducts in a patient who has had resection of a tumor of the bifurcation of the hepatic ducts.

anatomic definition is much more precise than with ultrasonography but the equipment needed to carry out this type of study is very expensive and accompanied by considerable irradiation (Figure 3). This technique is more effective than ultrasonography, especially in patients afflicted with much intestinal gas and those who are extremely fat. But the absence of fat in poorly nourished patients reduces the quality of the CT image. Both ultrasonography and CT scan play an important role in the evaluation of jaundice. Identification of dilated bile ducts usually, but not always, indicates the presence of bile duct obstruction and helps distinguish between obstructive and hepatocellular jaundice. Both of these techniques can be carried out in instances where oral and intravenous methods of cholangiography are useless. Most authorities prefer to use ultrasonography first, using computed tomography when inadequate images have been obtained by the other technique.[14,15] The fact that a CT scan study costs about four times that of an ultrasound study is another point in favor of ultrasonography.

Radionuclide Imaging

An important new tool for functional and anatomic imaging of the liver and biliary tree, especially in jaundiced patients, has been technetium 99m-labeled *N*-substituted iminodiacetic acid (Lidofenin, or HIDA). This substance is rapidly taken up by the liver and excreted in the bile ducts in sufficient concentrations so that the gallbladder and bile ducts can be seen as it accumulates there. One can evaluate the pickup of this substance in the liver, excretion by the bile ducts and accumulation in the gallbladder and its drainage into the intestine. It is possible to identify the gallbladder and bile ducts even in the presence of impaired liver function and serum bilirubin concentrations up to 7 to 8 mg per dl. This substance has a relatively short half-life, absence of beta emission and an ideal photon peak so that it can be given safely in high enough doses to obtain good images in a short time. The tech-

Figure 4.—Normal HIDA (Lidofenin) scan showing radioactive uptake appearing not only in the biliary tract but also in the duodenum.

Figure 5.—HIDA (Lidofenin) scan showing an obstructed distal bile duct and gallbladder with no radioactive uptake seen in the duodenum.

Figure 6.—Photograph of a percutaneous cholangiogram done on the same patient as in Figure 3, showing a dilated left hepatic duct.

nique's greatest value is in the evaluation of acute gallbladder attacks in which an image of the bile ducts appears and the gallbladder does not. It is 90 percent to 95 percent accurate in detecting acute cholecystitis in this situation. It also is useful in determining the presence of obstructive jaundice, wherein the material accumulates in the biliary tree and does not appear in the intestine, with an accuracy of 30 percent to 50 percent in four hours (Figures 4 and 5). In biliary atresia, it does not appear outside of the liver and a large image of the choledochus appears in choledochal cysts.[15-18]

Transhepatic Cholangiography

Percutaneous transhepatic cholangiography (PTC) was first carried out by Huard and Do-Xuan-Hop in 1937. Over the next 35 to 40 years it was rarely done because of the frequent complications of bile peritonitis, cholangitis and sepsis. Carter and Saypol[19] in 1952 placed a No. 17 spinal needle in the hepatic ducts, took x-ray films and used this needle as a drain. Ten years later, Arner and associates[20] were able to use an image intensifier so that even nondilated intrahepatic ducts in many situations can be seen.

A number of other approaches have been developed since then but a modified procedure that uses a long thin needle through the entire thickness of the right lobe of the liver appears to be the most suitable for nonsurgical patients and to have the least complications. Okuda and colleagues[21] at the Chiba University of Medicine carried out a large scale study using a 23-gauge needle with an outer diameter of 0.7 mm and a length of 15 cm that could be inserted into the liver percutaneously from the right midaxillary line. It was directed from the flank toward an area slightly above the junction of the right and left hepatic ducts with a patient on an image-intensification table, parallel to the table until the tip of the needle is positioned in the hepatic parenchyma to the right of the 12th thoracic vertebra. Contrast material is then injected slowly as the needle is withdrawn under image intensification. Contrast material runs away quickly when injected into the hepatic or portal veins, but persists in the hepatic ducts, outlines the ducts and moves slowly toward the common hepatic ducts. Insertion of the needle can be repeated safely several times until the bile ducts are seen. When the bile ducts are identified, enough contrast material is injected to fill the biliary tree and take multiple x-ray films (Figure 6).

Okuda and co-workers[21] in their initial series were able to examine the ducts of 54 of 80 patients with hepatobiliary problems and nondilated ducts. Sepsis developed in 11 of the 314 patients studied and the gallbladder was punctured in one patient. In studies carried out by Elias and colleagues,[22] cholangitis developed in two patients and in one a major leak of bile into the peritoneum after percutaneous cholangiography using this needle, both of these patients having marked dilatation of the biliary system. They were somewhat more successful in defining extrahepatic rather than intrahepatic cholestasis by percutaneous cholangiography. The group with intrahepatic cholestasis could be better defined using endoscopic approaches. Juler and associates[23] used percutaneous cholangiography in 30 patients with bile duct obstruction. They observed that 40 percent had bile leakage of 5 to 500 ml at laparotomy or autopsy and nine had peritonitis. They also observed that bacteremia developed in 23 percent. This study suggested that PTC with Chiba needle had little advantage over the larger sheathed needles and that surgical standby was required in suspected cases of obstructive jaundice. These patients should be given prestudy antibiotic agents such as cephalosporins.

Percutaneous Drainage

At this point, several authors[24-28] suggested that intubation of the hepatic ducts using a combination of the percutaneous transhepatic cholangiography technique and the Seldinger angiography catheter was satisfactory and the complications were few. A PTC using a 23-gauge needle was

carried out first. The needle was removed and an 18-cm long needle with an overlying thin-wall polyethylene catheter was installed, either in the same direction into one of the right intrahepatic duct branches or using a frontal approach under fluoroscopic control into one of the intrahepatic bile ducts of the left lobe of the liver. After bile was obtained, the needle was withdrawn and the sheath catheter was left in place through which a guide wire was inserted and positioned in one of the larger bile ducts at a suitable distance from its entry into the ductal system. The catheter was then withdrawn and a Seldinger catheter with several side holes at the tip, such as a Kifa Green catheter 1.2 mm in inner diameter, was introduced over the guide wire. The guide wire was then withdrawn and the catheter advanced farther down into the common hepatic duct.

A very large number of patients have now been reported on who had PTC of this nature with subsequent external bile drainage through tubes. This technique allows recovery of liver function and improvement in a patient's general condition before radical or palliative surgical intervention and nonsurgical palliation in advanced cases of malignancy; it also prevents postcholangiography leakage from the liver. In a series from Lund, Sweden,[25] emergency operation because of bile leakage despite established drainage of the bile ducts was necessary in only 3 out of 105 patients. In a series from Philadelphia,[24] the biliary tree was successfully catheterized in 41 of 43 cases of obstructive jaundice. Both of the failures could be traced to extensive occlusion of the intrahepatic ductal system by tumor. Once drainage was established, 22 of 39 patients had considerable reductions in total serum bilirubin at the rate of 2 mg per dl a day, with improvement in symptoms. Mean total serum bilirubin level dropped from 19.9 to 4.7 mg per dl. The major complication of percutaneous transhepatic catheterization was exacerbation of a preexisting infection with bacteremia in the obstructed ductal system despite antibiotic coverage after a "golden" period of three to five days.

Recent studies published by Ferrucci and colleagues[29] from the Massachusetts General Hospital advocate a variation of the techniques originally described by Hoevels, Ring, Nakayama and their associates.[26,30,31] They point out that guide wires of adequate caliber to support catheter exchanges will not fit the Chiba needle. For this reason, standard fine needle puncture should be followed by puncture with a special 15-cm 18-gauge sheathed cannula in a separate step. These authors have found the biliary catheter especially designed by Ring and co-workers,[30] a 40-cm long 8.3 French multiple-side-hole catheter with a tapered tip and a pigtail terminus, is most suitable for introducing into the distal duct or all the way into the duodenum. Complications occurred in 15 out of 62 patients, of which three were major. Other complications included one case of delayed subphrenic abscess and two cases of bleeding. The complications of catheter occlusion, bleeding through the catheter, unrelieved jaundice and sepsis due to dislodgement of the catheter have been discussed at some length.

A recent study[31] showed a 29 percent operative mortality in 148 severely jaundiced patients undergoing operation without prior decompression, in contrast to an 8 percent operative mortality in 69 patients undergoing preoperative transhepatic drainage. Further refinement of the above technique has made it possible to manipulate percutaneous transhepatic catheters through an obstructing lesion into the distal segment of the bile duct or the duodenum[24] to facilitate combined external bile drainage.

Based on this experience with temporary catheters, a nonsurgical technique of introducing a permanent Teflon bile duct endoprosthesis has been developed[25,26] This endoprosthesis is inserted following percutaneous transhepatic puncture and insertion of catheters into the bile duct system and can be left in place for long periods. They can be replaced if obstructed, displaced or compromised by cholangitis, all frequently occurring complications. It appears that nonsurgical insertion of a bile duct endoprosthesis may be the only palliative procedure in situations where there is a cytologically verified malignant tumor obstructing the extrahepatic bile ducts.[27] It is probably best suited for elderly patients with poor general condition, those with generalized malignant disease, those with metastatic tumor obstructing the bile ducts and those patients in whom a surgical procedure would be impossible for technical reasons.

Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) was first described in 1968 by McCune and colleagues[32] but did not become widely available until a year later when Oi and associates,[33] using a new duodenoscope, were able to cannu-

late the papilla of Vater with greater ease using a right-angle viewer rather than a straight-ahead instrument. A cannula is introduced from below, rather than above as in percutaneous cholangiography, for injection of radiopaque medium (Figures 7 and 8). This is primarily an imaging procedure for obtaining good x-ray studies of the biliary system.

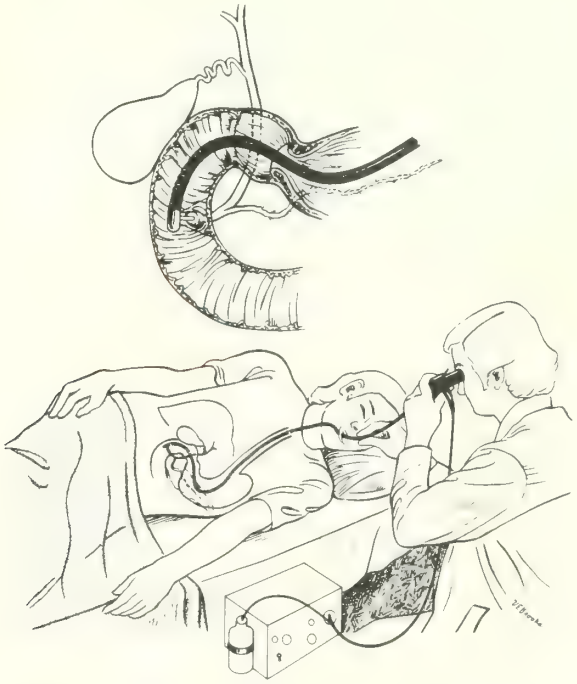

Figure 7.—Drawing showing the technique of endoscopic retrograde cholangiopancreatography (ERCP) from T. T. White and F. Silverstein (*Cancer* 1976 Jan; 37:449-461).

Figure 8.—Photograph taken during endoscopic retrograde cholangiopancreatography (ERCP) showing several stones in the distal bile duct.

Sepsis and pancreatitis are the two main hazards of retrograde injection, chiefly because of the increased pressure with injection.[34,35] Pancreatitis with some degree of elevation of serum amylase level occurs in most patients in whom the pancreas is opacified, especially when overopacification of the acini occurs. Sepsis occurs primarily in patients with poor drainage of the biliary tree. Many of the patients with stasis were already infected before the injection, with sepsis and cholangitis occurring because of dissemination of bacteria into the circulation as a result of the injection.[36] When there is poor drainage of the biliary tree, injection of contrast medium should be kept to a minimum with the aim of reducing the risk of cholangitis. Otherwise, injection should continue until the biliary tree and gallbladder are filled. Tilting the patient helps to fill the hepatic tree. A number of pictures should be taken because the radiopaque medium tends to layer, which produces distortion. Calculi float up the duct. Sclerosing cholangitis, strictures, carcinoma of the bile ducts and compression of the distal bile duct by carcinoma of the pancreas or chronic pancreatitis can be seen in the cholangiograms. It may be possible to diagnose lesions high in the biliary system by inserting a brush into the biliary tree by this route to obtain specimens for cytologic examination. Cancers of the lower bile duct or papilla are easily diagnosed by visual examination at endoscopy and easily confirmed by examination of cytology or biopsy specimens.[37,38]

This is an excellent approach for differentiating obstructive from hepatocellular jaundice and for observing both jaundiced and nonjaundiced patients after biliary surgical procedure for stricture, stone or normality. Evidence obtained in this manner can serve as a guide to the treatment of an obstructed bile duct, whether by surgical or endoscopic papillotomy, surgical drainage, other types of drainage procedures or medical therapy.[38] A good review article on this subject was written in 1977 by Cotton.[36]

Cephaloridine, cefazolin sodium, and gentamicin sulfate are useful prophylactic agents when given in conjunction with these procedures. Retained dye in the biliary tract or pancreas should be drained immediately.

Endoscopic Sphincterotomy

Retained and recurrent common bile duct stones through the years have required surgical treatment. Endoscopic sphincterotomy is an extension of ERCP first described in 1974 by Kawai and co-workers[39] and Classen and Demling,[40] and several thousand such procedures have since been carried out.[41-43] The key to doing this procedure is the use of a right-angle fiberduodenoscope such as is used for ERCP through which a sphincterotome, consisting of a wire drawn through the catheter used for papillary cannulation, is inserted into the papilla (Figure 9). The distal end of the wire is fixed to the tip of the catheter so that when it is pulled, the tip of the catheter bends so that a segment of the wire separates from the catheter, producing a sawlike wire that can be used as a cautery. A mixed cutting and coagulating current is used for sphincterotomy.

The first step of the procedure is selective retrograde cannulation of the biliary tract and injection of radiopaque medium for x-ray studies. After observing the ampulla and clarifying the anatomy of the biliary system, one advances the sphincterotome into the bile duct, establishing its position by fluoroscopy. The sphincterotome is then drawn back under visual control until the proximal end of the free portion of the wire is just outside the papilla. The direction of incision should then be upwards at the 10 or 11 o'clock position when facing the papilla. The average length of the incision in the bile duct should be 17 mm.

Common bile duct stones are removed with a Dormia basket catheter. The closed catheter is advanced beyond the calculi under fluoroscopic control, then the basket is opened and an attempt made to capture the stone and remove it from the bile duct. A captured stone can be pulled out of the duodenum along with the endoscope. The overall success rate of this technique is reported to be between 90 percent and 95 percent.

The main complications have been bleeding, retroperitoneal perforation, pancreatitis, cholangitis with an impacted stone and an impacted Dormia basket, with the total incidence of complications occurring in less than 7 percent of operations done. Emergency laparotomy has been required in somewhat less than 2 percent and the overall mortality of this procedure is less than 1 percent.

Endoscopic sphincterotomy was initially used only for postcholecystectomy patients who were elderly, poor risks or in whom there were technical problems. At present, high risk patients who still have their gallbladder and in whom acute obstructive cholangitis or obstructive jaundice can be relieved before cholecystectomy are being drained in this fashion. This converts a high risk patient to one who is a candidate for an elective cholecystectomy, with well-defined biliary anatomy showing residual stones that can be flushed out. This technique, however, should be carried out only in the hands of skilled endoscopists.[41-44]

Choledochoscopy

Choledochoscopy has gradually developed since Bakeš designed a speculum in 1923 for examining the interior of the bile ducts at operation. He used an instrument somewhat like the ones used to examine the vocal cords today. Later attempts were made in the 1930's to look at the interior of the gallbladder using a cystoscope. The first choledochoscope was described by McIver in 1941[45] and manufactured by the American Cys-

Figure 9.—Photograph taken during retrograde cholangiopancreatography showing endoscopic cannulation of the distal bile duct with the cutting wires in place for endoscopic sphincterotomy in the same patient as in Figure 8. The stones shown in Figure 8 were later successfully removed.

toscope Makers, Inc. (ACMI). This had a rather dim light with the intraductal portion of the instrument at right angles to the viewing arm. Another choledochoscope described by Wildegans and manufactured by Wolf had a 60-degree rather than a 90-degree angle. The most recent choledochoscope of this type was introduced by Storz using the Hopkins rod lens optical system, which gives a more effective optical function and uses a fiberopticlike carrier to furnish light. This rigid right-angle choledochoscope measures 3 mm in diameter and is 4 or 6 mm in length, depending on the model. An instrument guide channel can be attached for the passage of stone-retrieval instruments or biopsy forceps.

The first flexible fiberoptic choledochoscope was introduced by ACMI in 1965,[46] with an optical performance somewhat inferior to that of the rigid scopes previously introduced. More recently, several new models of flexible instruments with directable tips have been introduced by Olympus Optical Co., Fuji, Machida and ACMI[47] that can be used both at operation and through a T-tube tract. These instruments have been greatly improved over the early ACMI scope.

Figure 10.—Illustration of one of the several types of available flexible endoscopes for examining the interior of the bile duct. This particular one was manufactured by American Cystoscope Makers, Inc. (ACMI).

Techniques that not only locate gallstones in the common and hepatic ducts but also reliably ensure that no stones have been left behind are essential in the treatment of benign and malignant obstructive jaundice. Intravenous cholangiography, percutaneous transhepatic cholangiography and ERCP have been used for these procedures and for operative cholangiography.[48-50] The bile duct is explored when cholangiograms show the presence of filling defects or bile duct obstruction. The common bile duct has been blindly explored for years with a number of different types of forceps and probes that also gauge the diameter of the ampulla by feel. These instruments can easily extract a stone from the duct. Flushing has been used to help remove stones. One cannot palpate extremely small stones. The rigid choledochoscopes manufactured by Storz and Wolf have the advantage of good optics and good light, together with ease of use in determining visually whether or not further sludge, stones or calculi remain in the bile duct after instrumental removal. They also are useful in taking biopsy specimens from the interior of the ducts in cases of suspected malignancy. They cannot, however, reach far up into the hepatic ducts in search of stones and cannot be used during the postoperative period through a T-tube tract. The flexible choledochoscopes vary from 5 mm (ACMI) to 6 or 7 mm (Olympus, Fuji and Machida) and can be passed down a T-tube tract following T-tube drainage of the common duct.

The operative Olympus CHF-B3 flexible choledochoscope, which has appeared recently, is a considerable improvement over the earlier flexible scopes but it is difficult to advance down the duct, as are the instruments made by ACMI, Fuji and Machida. All four types of instruments have graded amounts of flexibility and directable tips.[47,51] This type of instrument appears to be much more useful for looking high up into the liver and into the bile ducts through a T-tube tract during the postoperative period following common bile duct exploration,[47,52,53] than for routine choledochoscopy at operation where the bulk of the stones are between the bifurcation of the hepatic ducts and the ampulla (Figure 10).

The fiberoptic flexible scopes cost from $4,000 (ACMI) to $6,000 to $7,500 each (Olympus, Fuji, Machida). The rigid choledochoscopes cost $1,500 to $2,000 each. These instruments can be used only once every 24 to 72 hours because of the need for gas sterilization and aeration.

Obstructive Jaundice Due to Gallstones

Gallstone disease is thought to occur in about 10 percent of the adult population in the United States and in about 20 percent of people over the age of 40. The incidence of cholelithiasis increases progressively with aging. Thus, gallstone disease is one of our most common illnesses, with about 500,000 cholecystectomies carried out yearly for this disease. The most common serious problem of gallstone disease is that of calculi in the extrahepatic biliary ducts causing obstructive jaundice and its complications. The overall incidence of bile duct calculi in patients undergoing cholecystectomy ranges from 7 percent to 15 percent in different series, so that approximately one out of ten patients with gallstone disease has choledocholithiasis at the time of the primary biliary operation. The treatment of obstructive biliary disease with or without cholangitis or jaundice has been simplified by the addition of ultrasonography and HIDA and CT scans, ERCP and percutaneous cholangiography, which provide a clearer definition of the problems faced by clinicians and surgeons. The routine management of stone-related jaundice still involves cholecystectomy, cholangiography, common duct exploration with removal of stones and drainage of the biliary tree.

Measurements of intrabiliary pressure during operation or manometric cholangiography have been carried out in Europe for years but have only recently been added to the armamentarium of American surgeons.[54,55] These techniques show small obstructions to outflow of the biliary system whereas x-ray studies show layer deformities and filling defects caused by the presence of stones.[56,57] Flow and pressure studies are easy to do and are useful in making a diagnosis of pathology of the distal bile duct, but still need to be standardized.

The various types of choledochoscopes described above have all been developed in the last ten years and are useful for locating stones in the duct system not ordinarily found by the blind techniques used in the past. The rigid choledochoscopes are useful for more routine cases where the stones are in the common hepatic and common bile ducts. The flexible types made by ACMI, Olympus and others are especially valuable for identification of stones in more remote areas of the biliary systems, such as high in the liver.[47-53]

A useful adjunct in the postoperative period has been the possibility of removing stones through a T-tube tract that have been missed despite careful exploration. Cholic acid[58] and, more recently, Capmul (a solvent manufactured by Stokely-Van Camp, Inc. and currently under investigation) have been introduced in an effort to dissolve cholesterol stones that have been left behind after common duct exploration. Also, simple irrigation of the T tube with saline or heparin will dislodge many of these stones into the duodenum. At the same time, as these new solutions have emerged it has become possible to pass steerable catheters down into the common

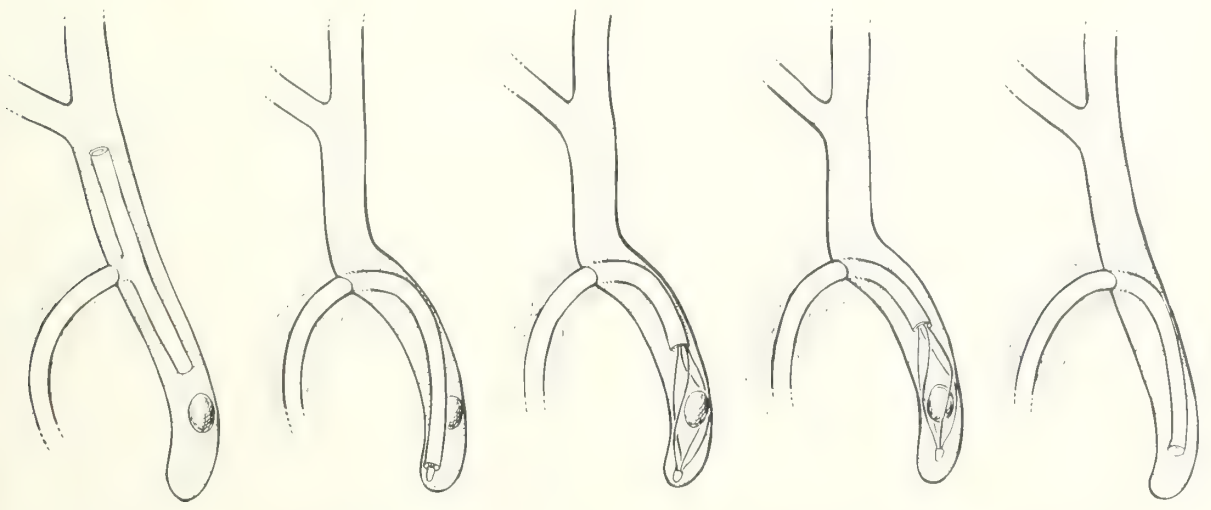
T-tube in place
Directional catheter inserted
Catheter retracted, stone basket open
Stone trapped in basket
Stone removed, catheter in place

Figure 11.—Diagrammatic representation of removing stones by a directable stone basket (from White and Harrison[2]).

bile duct under fluoroscopic guidance so that stones can be trapped with a Dormia basket and pulled out through a T-tube tract to the surface (Figure 11). This technique requires that the T tube left in the common bile duct following exploration be large enough to allow passage of instruments to the bile duct. At first this was done by putting a large catheter over the outside of the vertical arm of the T tube.[59,60] T tubes are now available in which the vertical arm is four sizes larger than the part inserted into the duct, allowing a relatively small tube to be placed in the duct with a larger branch extending to the surface. A part of this technique requires that the vertical arm be run laterally so that with a patient in a supine position a radiologist can see the instrument passing through the tract without overlapping the bile duct. With this approach one must wait six to eight weeks after the operative procedure to allow formation of a solid tract that will not be damaged by instruments.

At the same time that this technique was being developed, surgeons, internists and radiologists discovered that a fiberoptic bronchoscope could be passed down through a T-tube tract into the common bile duct for extraction of stones. The special choledochoscopes described above are useful for extracting stones under direct vision in the postoperative period.[51] At present, it appears that the mechanical methods of extraction of stones in the postoperative period are more efficient than those of chemical dissolution.

The nonoperative approaches to decompression in patients with advanced obstructive jaundice, cholangitis or both constitute additional spectacular advances in the past ten years.[23-31] Percutaneous drainage of the biliary tree and endoscopic sphincterotomy and drainage of this system have progressed to the point that this approach is available in a great many major centers of the United States by physicians faced with the emergency treatment of a severely debilitated patient with overwhelming jaundice and sepsis. Definitive operative procedures can be carried out when a patient is in reasonably good general condition.

Less severely ill patients are treated as before. We have the alternative, however, of doing endoscopic sphincterotomy and drainage of the biliary tree postoperatively and in unoperated patients who do not have a T tube in place, as well as in those with stones that cannot be extracted through a T-tube tract. The approach used should be dictated by the availability of experts in the use of these techniques. Standard techniques of cholecystectomy or drainage of the common bile ducts should be used whenever the newer techniques are not available. Whichever method is used, emergency drainage of the common bile duct for septic cholangitis should always be carried out. Orloff[61] reports that "the exact incidence of retained and recurrent bile duct stones is not known because most patients who undergo cholecystectomy with or without choledocholithotomy are rapidly restored to good health. There have been no thorough long-term postoperative studies on selected patients with gallstone disease. Most of the available data on the incidence of residual stones has been obtained during the early postoperative period and most of it has been based on cholangiography performed through a T tube in the common bile duct within two weeks of operation."[61(p104)]

The rate of retained calculi following a common bile duct exploration has been consistent, ranging from 10 percent to 13 percent of patients, while that following negative findings at choledochotomy has been substantially lower. Because these observations have been confined to the immediate postoperative period, the true incidence of retained and recurrent bile duct stones is undoubtedly higher. The incidence of residual choledocholithiasis following cholecystectomy without common bile duct exploration is unknown, but it appears to be quite low. Thus, there continues to be a prevalence of residual common bile duct stones found from several days to several years after the initial operative procedure despite more than adequate critical experience throughout the world pertaining to the removal of common bile stones. Most of these stones have been thought to be retained. For this reason, efforts should be made to discover the actual incidence of retained stones by carrying out cholangiography, manometry, choledochoscopy and other procedures. The incidence of secondary operations at various institutions varies from 2 percent to 7 percent, the greatest incidence being for retained and common bile duct stones and strictures, followed closely by cancer and pancreatitis.

Biliary obstruction due to either benign or malignant disease has been relieved by four major approaches, cholecystenterostomy, choledochoenterostomy, dilatation of the sphincter of Oddi and transduodenal sphincteroplasty. The gallbladder has been used as a drainage route for over 100 years. A recent study carried out by Dayton and

colleagues[62] showed that cholecystenterostomy failed in 5 out of 59 cases of malignancy and 4 out of 17 of benign disease for an overall failure rate of 12 percent. Our own studies suggest an even higher failure rate of nearly 20 percent.

Bakeš hoped that ampullary dilatation using a series of dilators bearing his name would allow any retained stones to pass after exploration of the common bile duct. Whereas early studies indicated that dilatation practically eliminated the possibility of residual stones, later authors such as Jones and Smith,[63] Kune and Sali[5] and Heimbach and White[64] have noted the ineffectiveness of dilatation in preventing retained and recurrent stones and have felt that transduodenal sphincteroplasty of choledochoduodenostomy were preferable to dilatation of the sphincter. Lateral choledochoduodenostomy has been reported by Rodney Smith[65] to result in a sump syndrome in over half of 250 cases reported on by another London surgeon. He has carried out transduodenal sphincteroplasty on those patients, with considerable long-term success. Kune and Sali[5] and this author have noted similar problems and solved them in the same way. These and other procedures on the biliary tract have never really been studied in a prospective fashion. It appears now, however, that it may be possible to eliminate most of the retained and residual stones appearing in the late postoperative period using endoscopic sphincterotomy. This approach has been used with increasing frequency, with the result that some recent publications suggest that endoscopic sphincterotomy is the procedure of choice for retained and residual stones.[41-44]

Strictures of the ampulla of Vater and the lower end of the common bile duct are usually sequelae of the passage of multiple stones from the biliary system into the intestine. Such strictures can be the cause of primary common bile duct stones with secondary jaundice, dilatation and cholangitis and may occur both primarily and after common duct exploration. Stenosis of the sphincter of Oddi has been described in two different ways, one suggesting that actual fibrosis of the sphincter has occurred and the other that there is inflammation of the sphincter and spasm.

The diagnosis is made frequently in Europe and South America and much less frequently in North America.[2] There is considerable ambiguity as to what this condition actually consists of. Names such as ampullary fibrosis, distal stricture, fibrosis of the sphincter, vaterian segment obstruction, phimosis of the ampulla, chronic odditis and chronic papillitis have been used. Patients with this syndrome usually have a common bile duct more than 15 mm in diameter and intermittently may have elevated serum bilirubin or serum alkaline phosphatase levels or both, especially after the injection of a stimulus to bile secretion such as secretin. The ducts are found to be dilated on ultrasound studies and percutaneous cholangiograms, the ampulla can be cannulated only with difficulty on ERCP and there are common bile duct stones present in about half of the cases. Patients with spasm or dyskinesia, however, have a normal duct size with easy cannulation by ERCP and without jaundice, chemical abnormality or stones in the bile duct. Attempts have been made in recent years to measure sphincteric pressure using balloons or perfusion with saline during ERCP cannulation. It is not clear as yet what the best treatment of spasm or dyskinesia is and whether it is necessary to go as far as in the treatment of papillary stricture and stenosis.

Cases of clear-cut stenosis or stricture of the bile duct are now usually evaluated preoperatively by percutaneous cholangiography or ERCP. Manometric cholangiography can be carried out intraoperatively and will show intrabiliary pressure of over 20 cm of water, low flow and obstruction in the distal bile duct. It will also be difficult or impossible to pass a No. 3 Bakeš dilator through the sphincter. There has been considerable discussion as to whether these secondary patients are best treated by choledochoduodenostomy, transduodenal sphincteroplasty or endoscopic sphincterotomy. Most patients are being treated with one or the other of the two former procedures, with some physicians advocating endoscopic sphincterotomy for more debilitated patients.[43,44]

If an operative procedure is to be carried out, there are certain special considerations that cause one to choose a sphincteroplasty rather than a choledochoduodenostomy (Figure 12).[63,66,67] A patient found at exploration to have not only a stricture of the ampulla but also coexistent pancreatitis that is not constricting the intrapancreatic portion of the bile duct should have a sphincteroplasty with division of the pancreatic duct sphincters.

A patient with substantial narrowing of the intrapancreatic bile duct should have a choledochoduodenostomy because the sphincteroplasty would in this situation be below the point of biliary obstruction. Sphincteroplasty is preferable

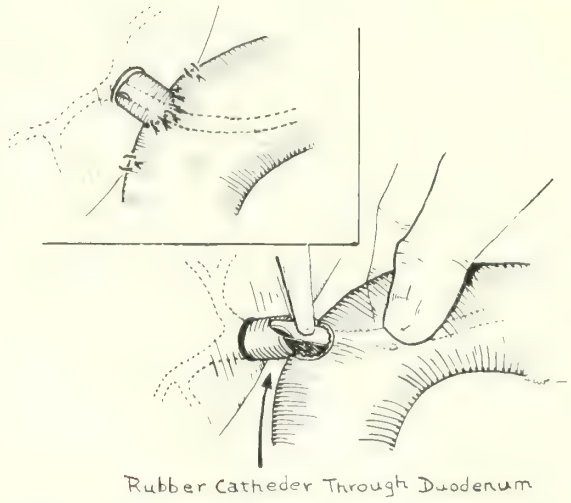

Figure 12.—Artist's drawing of a technique of choledochoduodenostomy.

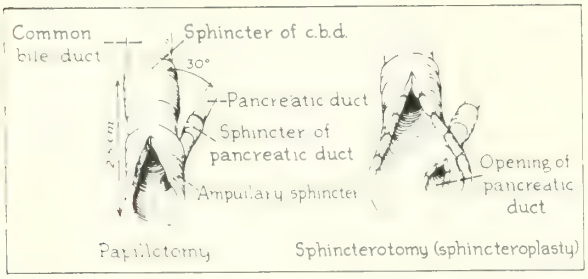

Figure 13.—Papillotomy is a quicker method of removing small stones. An incision of about 2.5 cm is required to cut the entire sphincter mechanism.

when the duodenum must be explored because of suspicion of some form of intraduodenal malignancy or because a stone is impacted in the distal end of the bile duct and cannot be retrieved otherwise (Figure 13). It is also the preferred procedure when there is associated pancreatitis without compression of the distal duct. A choledochoduodenostomy is preferable whenever the distal intrapancreatic bile duct is narrowed. We prefer to do a sphincteroplasty when the duct is less than 15 mm in diameter, a choledochoduodenostomy or sphincteroplasty when it is between 16 and 25 mm in diameter and a choledochoduodenostomy in larger ducts.[68,69]

A sphincteroplasty must be long enough to make the opening between the bile duct and the duodenum roughly the same as the largest diameter of the bile duct above. Under these circumstances one of these operations is preferred to choledochojejunostomy, because of the metabolic consequences of placing the anastomosis lower. This approach is valuable, however, for stricture.

The most catastrophic complication of a straightforward cholecystectomy is that of accidental ligature of or injury to the common or hepatic bile duct. This usually preventable technical error is fairly rare, having occurred in 336 of 63,252 cholecystectomies done in 1973 in the state of Ohio.[70] This diagnosis should be made during or immediately after the operation but there may be no jaundice or biliary fistula and several weeks and, uncommonly, several months or years may go by before stenosis develops to the point that stricture or jaundice occurs and reoperation is required. Most such injuries are evident early by the presence of a bile fistula with accompanying jaundice, rather than jaundice alone, so that most repairs can be done during the first four to six weeks after the initial procedure. A patient who is reexplored during the first four to six weeks is often debilitated because of cholangitis and occasionally abscess formation. Under these circumstances, the biliary tract should be decompressed with catheters or a T tube and the definitive repairs postponed until infection and jaundice have subsided.

Only in rare instances where there is redundant duct that allows an end-to-end anastomosis should a biliary anastomosis be carried out. Longmire[68] reported that 11 of his 22 end-to-end anastomoses failed. The preferred approach, therefore, appears to be to anastomose the damaged bile duct to a Roux-en-Y jejunal loop both early and late (Figure 14). The anastomosis is made with either end of the bile duct to the side of the jejunum or end to end, most surgeons preferring the former. This is relatively simple when the bile duct projects sufficiently below the liver so that a good extrahepatic anastomosis can be carried out.

The anastomosis is drained internally and splinted by means of a T tube placed through the bile duct where there is enough bile duct available below the bifurcation. If the suture line is closer to the junction of the right and left hepatic ducts, the upper portion of the tube can be split. Alternatively, transhepatic tubes can be placed through both the right and left hepatic ducts where the proximal portion of the tube has been brought out through the liver parenchyma and out through the abdominal wall, as described by Cameron and co-workers,[71] Praderi,[72] Saypol and Kurian[73] and Smith.[74] These approaches have worked best when a very large tube (1 cm in diameter) was passed through the damaged or strictured area but have

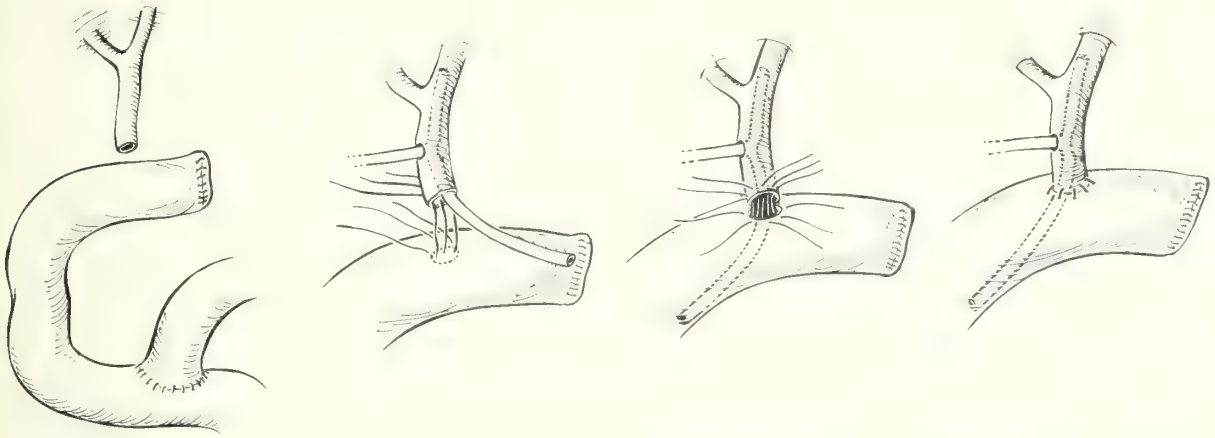

Figure 14.—Artist's drawing showing technique of choledochojejunostomy for decompression of bile duct strictures in which the damaged bile duct is anastomosed to a Roux-en-Y jejunal loop. (Reproduced with permission from White and Harrison.[4])

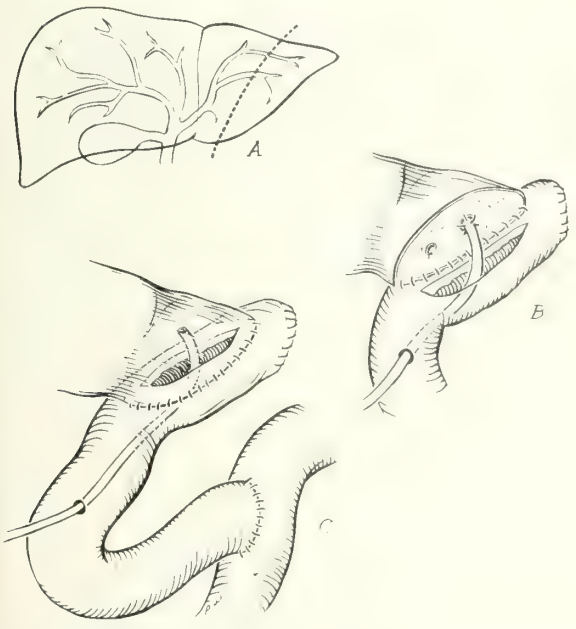

Figure 15.—The Longmire operation for high bile duct strictures. (Reproduced with permission from White and Harrison.[4])

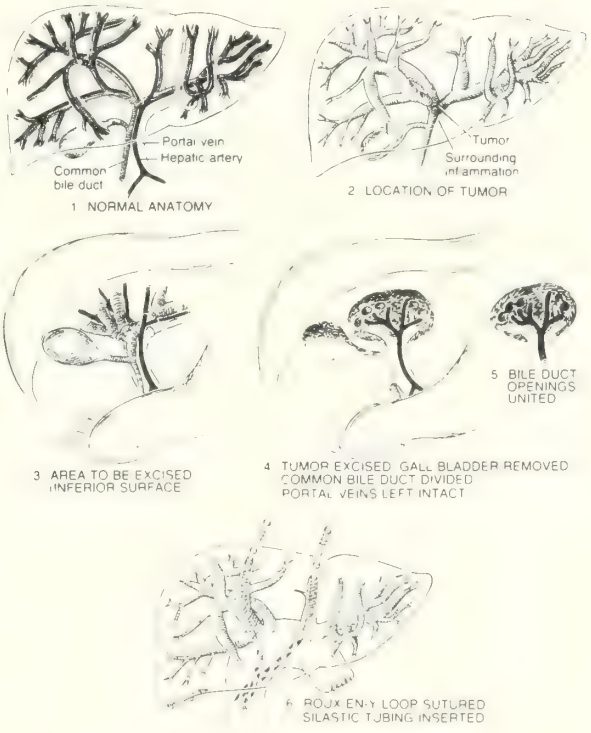
Portal vein
Hepatic artery
Common bile duct
1 NORMAL ANATOMY
Tumor
Surrounding inflammation
2 LOCATION OF TUMOR
3 AREA TO BE EXCISED INFERIOR SURFACE
4 TUMOR EXCISED GALL BLADDER REMOVED COMMON BILE DUCT DIVIDED PORTAL VEINS LEFT INTACT
5 BILE DUCT OPENINGS UNITED
6 ROUX EN-Y LOOP SUTURED SILASTIC TUBING INSERTED

Figure 16.—Technique of central hepatic resection for bifurcation tumors and strictures. (Reproduced with permission from Hart and White.[75])

the disadvantage of requiring daily injections to flush out debris. Further, they are often complicated by cholangitis and bleeding.

Another approach suggested by Longmire[68] is of Roux-en-Y anastomosis of one of the lateral intrahepatic ducts to a jejunal limb after a lateral segment of liver has been resected (Figure 15). We prefer removing either the entire central portion of the liver and then making an anastomosis to the several hepatic branches (Figure 16),[75] or using the technique devised by Bismuth and Corlette[76] of removing a portion of the liver to expose the main hepatic ducts away from the hilus, then making the anastomosis.

Cholangitis and Sepsis

Human bile is normally sterile but has been found to be contaminated in most patients with obstructive jaundice, common duct stones without jaundice, acute cholecystitis and patients over 60 years of age regardless of the type of pathologic

condition found.[77] Positive bile cultures are found at an increasing rate with advancing age even when only uncomplicated gallstones are present, with the result that 33 percent of patients over 70 have positive bile cultures.[78] There appears to be general agreement that patients with obstructive jaundice or anyone undergoing manipulation of the bile ducts, whether by common bile duct exploration, percutaneous cholangiography or ERCP, should have prophylactic antibiotic therapy. Cephaloridine given just before the procedure has been proved effective in reducing wound sepsis and septicemia.[79] Other effective regimens have been described using cefazolin[80,81] and gentamicin.[82] A single-dose regimen seems adequate in routine cases, rather than the three doses originally proposed by Polk and Lopez-Mayor,[83] but should obviously be continued for a long course in septic patients.

Sclerosing Cholangitis

Another type of obstructive jaundice that is confused with both primary biliary cirrhosis and carcinoma of the hepatic ducts is sclerosing cholangitis. This is an uncommon disease characterized by obliterative inflammatory fibrosis of the extrahepatic ducts, with or without involvement of intrahepatic ducts.[84,85] Patients with the following conditions are eliminated from this classification: jaundice due to drug or viral hepatitis, progressive obstructive jaundice, common duct stones, prior bile duct surgery or malignancy. All of these patients have thickening and fibrosis of the extrahepatic and sometimes the intrahepatic bile ducts. Most patients are between ages 30 and 50. Most patients are men, rather than women, as seen in primary biliary cirrhosis.

Tests of antimitochondrial antibody will show low antibody levels with sclerosing cholangitis, unlike levels found with primary biliary cirrhosis. Diagnosis has been made chiefly at surgical procedures in the past[86,87] but now can be readily made by either ERCP or transhepatic cholangiography.[88] The association of this disease with inflammatory bowel disease was reported by Warren and associates[89] and is increasingly reported to be so, with 54 percent of Wiesner and LaRusso's patients and 75 percent of Chapman and co-workers'[90] patients having associated inflammatory bowel disease.

Elevated serum copper levels are also reported with this disease, the role of which is unknown.[91] Jaundice and pruritus can be alleviated with the use of cholestyramine resin, which binds with bile and prevents its recirculation, and with corticosteroids.[92] Drainage by choledochoenterostomy or T tube is effective if appropriately established. It has been suggested recently (S. I. Schwartz, MD, oral communication, May 21, 1981) that percutaneous transhepatic drainage of the biliary system combined with the administration of corticosteroid, antibiotic and immunosuppressant drugs might be quite successful in treating these patients. It has also been suggested that colectomy might be of benefit in the treatment of sclerosing cholangitis in patients with associated inflammatory bowel disease, but the number of patients this has been done on is small. Dickson and associates[93] have suggested that penicillamine might be effective.

Most authors now think that this condition is an autoimmune reaction in the wall of the bile duct, rather than a bacterial or viral infectious disease. Association with retroperitoneal fibrosis, Riedel's thyroiditis, ulcerative colitis and regional ileitis suggest that this may indeed be the cause of the process. Positive diagnosis unfortunately requires a full-thickness biopsy specimen of the bile duct wall. Again unfortunately, most patients who have been observed for long periods die, but this may have been due to the fact that in the past only those in advanced stages of the disease were seen. Earlier cases are now being found by ERCP and percutaneous cholangiography.

Cancers of the Extrahepatic Bile Ducts and Head of the Pancreas

Cancers of the extrahepatic bile ducts occur relatively infrequently, consisting of less than 1 percent of all carcinomas and about 3 percent of gastrointestinal malignancies. A special handicap to the study of biliary cancer has been the failure of the International Classification of Diseases to distinguish between cancers of the liver and biliary system until the seventh revision in 1958. Since then about 4,500 deaths from cancers of the biliary tree have been reported yearly in the United States, as contrasted with 18,000 from pancreatic cancer. It appears that the incidence of biliary tract cancer is much higher among some racial groups than others, with Japanese having about five times the incidence of Caucasians.[94,95] The true epidemiologic makeup of this disease still remains to be clarified.

These tumors have been grouped anatomically into the following three groups according to the relative difference in prognosis of the lesions:

group 1, the upper region, including the left and right hepatic ducts and the confluence of the common hepatic duct; group 2, the common bile duct and the region of the cystic duct down to the pancreas; and group 3, the intrapancreatic portion of the common bile duct, including tumors of the ampulla of Vater.[96]

Group 3 carcinomas of the distal bile duct and pancreas may arise from the ampulla of Vater or duodenal epithelium. They may appear grossly as a polypoid growth replacing the ampulla or as an ulcer involving the same area. It is this group about which the most is known from the point of view of prognosis and treatment. They have often been grouped with carcinomas of the head of the pancreas. While they were originally treated by local resection and reimplantation into the duodenum, pancreaticoduodenectomy was first recommended for this lesion by Whipple and coworkers[97] in 1935 as a two-stage procedure. At present it is usually carried out in one stage, sometimes preceded by endoscopic sphincterotomy or by percutaneous drainage of the liver.

Pancreaticoduodenectomy is not an indicated treatment for the tumor in patients with metastases to the liver or regional lymph nodes. The mortality from this procedure has been as high as 50 percent as recently as ten years ago but shows signs of falling to about 10 percent in the hands of groups carrying out fairly large numbers of these procedures. Long-term survival over five years has been observed in around 35 percent of patients undergoing resection, which is the best outlook for survival of the various biliary tract cancers. In cases with long-term survival enough steatorrhea usually develops to require pancreatin supplements. Marginal ulcers at the site of gastric resection have developed in a number of patients and diabetes is an occasional complication.

Cases of group 2 and 3 carcinomas involving the area above the pancreas present different diagnostic and technical problems from those of the periampullary area. These have been confused with cases of gallstone disease and sclerosing cholangitis in the past, before the advent of ultrasonography, ERCP and percutaneous cholangiography.

Malignant tumors of the extrahepatic biliary tree have been noted in the past for late diagnosis in which radical cure was the exception and the prognosis was very bad. A series of 77 patients reported by Warren and colleagues[98] showed that only a third (24) had a radical procedure, 17 patients survived for more than a year and five were alive after three years. A disappointingly low survival rate has been reported in several other series.[95,99-102] Information has been scant as to the overall resectability, but some authors have reported that only a tenth to a quarter of patients are resectable at the time of laparotomy.

Jaundice has been the most important symptom of bile duct tumor and occurs quite early. The tumors are generally quite small because the lumen of the bile duct is relatively small to begin with. Other symptoms of bile duct cancer are insignificant compared with those of jaundice. Patients also have right upper quadrant abdominal pain and sometimes colic. The average duration of symptoms is two to three months. Physical examination will show an enlarged firm liver with a large gallbladder when the tumor is distal to the cystic duct or obstructing the cystic duct, causing hydrops of the gallbladder rather than Courvoisier-Terrier syndrome. Laboratory examination will show extrahepatic ductal obstruction. Ultrasonography shows dilated common hepatic and intrahepatic ducts. Both percutaneous cholangiography and retrograde cannulation of the ampulla of Vater will show the location of the tumor.

Particular attention was directed to tumors of the bifurcation of the hepatic duct by Klatskin in 1965.[103] At that time he reported 13 cases of adenocarcinoma of the hepatic duct, with advanced liver failure terminating in coma as the immediate cause of death, and he pointed out that hepatobiliary infection was the major factor in the deaths of most of these patients. He also noted that only 5 of the 13 patients had clinical evidence of metastasis at the time the diagnosis of carcinoma was made. He also pointed out that patients whose livers were decompressed lived an average of 23.3 months, as opposed to 9.9 months when the liver was not decompressed. Some authors have emphasized that these tumors should be bypassed or excised to prevent cholangitis,[104] and other publications have appeared describing methods of palliation or resection, including complete excision with end-to-end anastomosis and reconstruction of the biliary tree.[105]

The most common type of palliation in the past has been dilatation of the lesion with probes and splinting over a T tube, with resection being possible in only a relatively small number of patients, though major hepatic resection was possible in some patients.[106,107] The problem with this approach was that the T tubes became occluded

over a period and could not be replaced without reoperation. Terblanche[105] described the path of a U tube through the bile duct tumor and out through the liver, which could be replaced at will in a physician's office or in an x-ray department by simple railroading without the need for further operative procedure. This simple operative procedure resulted in the survival of some of his patients for six years or longer.

Tumors treated by the placement of U tubes extending through the liver and brought out through a Roux-en-Y loop have been offering fairly good palliation for periods of one to six years in reports from Cameron and colleagues.[71] We have found, however, that these tubes need to to be changed frequently, with considerable discomfort to the patient, and that it is possible to locally resect tumors of the hepatic ducts and bifurcation of the hepatic ducts and extend the excision up into the secondary hepatic ducts so as to achieve not only palliation but potential cures in some of these patients (Figure 16). Transhepatic tubes are used as a stent.

Attempts to excise these tumors have met with various success, with reports coming from Japan, France and the United States the past five years and articles by Corlette and Bookwalter[108] and Hart and White,[75] as well as several others.[107,109] At the present time a number of surgeons (including this author) are carrying out resection of the middle portion of the liver high up into the secondary ducts with bilateral hepaticojejunostomy, with some patients surviving without evidence of disease for as long as five years (Figure 16). Other authors are advocating resection of the right or left lobe of the liver, together with the portion of the upper bile ducts involved by tumor, and a third group of individuals is advocating removal of a portion of segment four or five in the right lobe. Also, many patients are still being treated with a U tube placed through the common and hepatic bile ducts to the anterior surface of the liver. Finally, percutaneous drainage is being used to decompress some patients in whom the diagnosis of carcinoma of the bile ducts has been made on the basis of percutaneous biopsies in tumors that appear very large on CT scan and ultrasound studies.

All of these approaches include decompression of the biliary tree, which results in fewer problems of sepsis, cholangitis and liver failure. The third, fourth and fifth approaches can be supplemented by radiation therapy, which appears to offer short-term palliation to these individuals, lengthening life for as long as six months to a year. Intraoperative radiotherapy has been advocated for patients with carcinoma at the hilus of the hepatic bile duct that involves the common hepatic artery or portal vein or that spreads to both right and left intrahepatic bile ducts (when its size does not extend beyond the field of radiation). Under these circumstances, laparotomy is carried out and external drainage is applied to relieve jaundice. A treatment cone is then positioned directly at the site of the tumor, the correct position is determined and radiotherapy is administered with an electron beam from a Betatron or linear accelerator, with a single dose of 3,000 rads and 11 to 18 meV delivered to the lesion. All patients treated thus by Iwasaki and associates[106] had slight relief of bile duct obstruction.

Another approach is that of placing radioactive gold seeds around the tumor at the time of operation. Combined with external radiotherapy, this may be of some value. The place of radiation therapy in cancer of the extrahepatic biliary system is being evaluated, both in the United States and Japan, from the point of view of curative therapy postoperatively to decrease local recurrences and increase the length and quality of survival and to treat incisional recurrences. In advanced disease management the aim is to increase the effectiveness and length of palliation and, in conjunction with chemotherapy, to further consolidate therapeutic gains made with radiotherapy alone.[110-113]

Pancreatic Cancer and Pancreatitis

Cancer of the pancreas is asymptomatic in its earliest stages; later it is evident by epigastric or back pain, jaundice and weight loss. Jaundice and a palpable gallbladder are usually the only physical findings in early cases. The same type of studies are used to diagnose obstructive jaundice on this basis as are used for the diagnosis of pancreatic cancer. A number of collaborative studies have been carried out on the diagnosis of pancreatic cancer using ultrasonography, computerized tomography, radionuclide scanning, ERCP, selective celiac and superior mesenteric angiography, duodenal drainage studies, cytologic studies and serum carcinoembryonic antigen and pancreatic oncofetal antigen assays. Most test findings have shown that a patient had either pancreatic cancer or pancreatitis. Cytologic examination with a positive result confirmed the presence of cancer

but only about a third of patients were thereby correctly diagnosed. If a negative result is taken to indicate pancreatitis, then 99 percent of all patients were diagnosed with a 75 percent accuracy.

Comparative results between ultrasound and CT scans have shown little difference. Ultrasonography is preferred on the basis of cost effectiveness but a combination may be more useful. ERCP was more accurate than duodenal drainage studies. Angiography is invasive and time-consuming and there is some difficulty with it in distinguishing between cancer and pancreatitis. Blood tests have been largely nonspecific. Therefore, gray-scale ultrasonography is probably the best noninvasive test for differentiating between pancreatic cancer and pancreatitis. CT scans are as good or superior but are more expensive. Other types of imaging procedures contribute little to this differentiation. ERCP is probably even more accurate and better at differentiating among the diagnoses of chronic pancreatitis, cancer and other lesions in this area.[114-117] The general treatment of pancreatic cancer and chronic pancreatitis is outside the realm of this paper, but jaundice in advanced cases can be treated as described earlier. The jaundice due to compression of the distal duct by chronic pancreatitis can be treated by choledochoduodenostomy or choledochojejunostomy.

Congenital Diseases of the Biliary Tract

Biliary Atresia

Congenital biliary atresia had been poorly defined up until 30 years ago. In 1953 Gross[118] reviewed 198 patients with obstructive jaundice, 183 of which were treated surgically, 26 successfully, for inspissated mucus or bile in the ducts that was treated by manipulation and irrigation of the ducts.[68] Only 12 of these patients had adequate biliary drainage achieved by duct-enteric anastomosis. Only 53 (26 percent) were relieved by medical or surgical therapy for a year or more.

There has been considerable question as to the cause of this type of lesion, whether it was due to arrested development during a solid stage, to a variety of congenital or developmental anomaly or to some type of hepatitis or cholangitis. Treatment in former years was one of delay of operation until the jaundice, if due to hepatitis, could have cleared. After the introduction in 1959 of a procedure for hepatic portoenterostomy by Kasai and associates,[119] emphasis has been on early operation, preferably in the first one to two months at a time when it is still impossible to differentiate the hepatitis of newborn from congenital biliary atresia.

Experience with this operation has encouraged the notion that neonatal hepatitis and extrahepatic atresia are different results of a single basic process occurring immediately after birth.[120] The suggestion is that the process is probably viral in origin, causing inflammation with varying degrees of liver cell and duct epithelial injury, followed by obliteration of the bile ducts and later scarring. The suggestion is that the progressive scarring of the ductal system may be halted or even reversed by resection of the extrahepatic ducts, combined with a bile drainage procedure such as has been proposed by Professor Kasai and co-workers.[119] The possibility that many of these cases are the result of an obstructive cholangitis of varying degrees rather than an unalterable developmental anomaly gives a different point of view relative to the outcome.

It is difficult to separate the congenital from the inflammatory type of biliary atresia at the present time. Kasai attempts to enhance biliary drainage by removing all of the obstructed or potentially obstructed extrahepatic ductal system and draining the hepatic ducts into a defunctionalized loop of jejunum. Lilly,[121] A. H. Bill, MD (personal communication, April 28, 1981) and many other surgeons throughout the world have confirmed the presence of bile duct drainage from the liver following this procedure for jaundice of newborns. Kasai and associates' first patient was alive and well 18 years later. Twenty out of Kasai's 80 patients were alive without jaundice, 14 for more than two years after operation in one recent report.[119] The main problem with this procedure has been one of postoperative cholangitis that in turn may lead to cirrhosis and portal hypertension even after decompression and relief of jaundice.

Miyata and colleagues[122] reported that 15 of 51 patients were completely relieved of jaundice, portal hypertension developed in 7 of the 15 and 4 died. Most of the patients later showed transient episodes of cholangitis. Also, in a substantial number of patients who were relieved of jaundice cirrhosis of the liver later developed and they died of their disease. It is still unclear as to the dividing line between true extrahepatic atresia on a congenital basis with intrahepatic changes comparable with acquired biliary obstruction in older people, biliary hypoplasia with varying degrees of reduction in size of the extrahepatic ducts with intrahepatic cirrhosis and those with inflammatory

neonatal hepatitis. It seems logical that most cases of neonatal jaundice, excluding rare, truly developmental anomalies, are the result of an ongoing or dynamic process, possibly similar to sclerosing cholangitis in adults. The overlap between hepatobiliary pathology and the clinical course makes it very difficult to clearly differentiate those patients with inflammatory neonatal hepatitis from those with congenital atresic malformations.

Biliary Cystic Dilatation

The current classification of cystic dilatations of the intrahepatic and extrahepatic biliary systems was suggested by Alonso-Lej in 1959, discussed by Flanigan[123] in 1975. In this classification, type I cysts, or about 80 percent of the total, include dilatations of the common bile duct and common hepatic duct. Subgroups IA, IB and IC were described later. The rare type II cysts are diverticula of the common bile duct.[123] Type III cysts, or choledochoceles, are intraduodenal cystic dilatations of the terminal common bile duct that may be lined by either duodenal or bile duct mucosa. Intrahepatic cystic dilatations that present alone or in combination with extrahepatic dilatation are now called Caroli's disease.[124] Choledochal cysts with clinical signs of right upper quadrant pain, obstructive jaundice and a mass are obvious in about a third of patients and the diagnosis is obscure in the others.[125,126] About a third of reported cases come from Japan; three quarters of patients are female. A fourth of such cysts are discovered before the age of one and 60 percent before the age of ten. The diagnosis was formerly made chiefly at operation but, with the advent of ultrasound and ERCP, most such patients are now diagnosed preoperatively.[124,127]

Type II and III cysts have been and are still simply excised and managed by internal drainage. Type I cysts were formerly treated mainly by internal drainage procedures to the stomach duodenum but now are treated by excision and anastomosis to a jejunal loop.[125,128] The complications that arise in unoperated patients include cholangitis, common bile duct stone formation, common bile duct stricture, obstructive jaundice, portal hypertension, biliary cirrhosis, rupture of cysts, development of bile duct cancer and pancreatitis.[129,130] It is for this reason that external rather than internal drainage and excision with anastomosis to a Roux-en-Y loop are now carried out. This procedure seems at the present time to be the treatment of choice. It is possible, however, to leave the posterior wall of the cyst in place to avoid injury to the structure. In this case the cyst wall is opened anteriorly and the lining of the cyst in the anterior and lateral walls is removed. Reconstruction is then carried out with an hepaticojejunostomy or choledochojejunostomy.[125,129]

REFERENCES

1. Schein CJ: Postcholecystectomy Syndromes—A Clinical Approach to Etiology, Diagnosis & Management. Hagerstown, MD, Harper & Row, 1978

2. White TT, Sarles H, Benhamou J-P: Liver, Bile Ducts, and Pancreas. New York, Grune & Stratton, 1977

3. Bouchier IAD (Ed): Diseases of the biliary tract. Clin Gastroenterol 1973; 2:1-215

4. White TT, Harrison RC: Reoperative Gastrointestinal Surgery, 2nd Ed. Boston, Little, Brown, 1979

5. Kune G, Sali A: Current Practice of Biliary Surgery, 2nd Ed. Boston, Blackwell Scientific, 1980

6. Berk RN, Clemett AR: Radiology of the Gallbladder and Bile Ducts. Philadelphia, WB Saunders, 1977

7. Ferrucci JT Jr: Body ultrasonography. N Engl J Med 1979 Mar 8, Mar 15; 300 (10,11):538-542; 590-602

8. Behan M, Kazam E: Sonography of the common bile duct: Value of the right anterior oblique view. AJR 1978 Apr; 130: 701-709

9. Cooperberg PL, Li D, Wong P, et al: Accuracy of common hepatic duct size in the evaluation of extrahepatic biliary obstruction. Radiology 1980 Apr; 135:141-144

10. Deitch EA: The reliability and clinical limitations of sonographic scanning of the biliary ducts. Ann Surg 1981; 194:167-170

11. Ulreich S, Foster KW, Stier SA, et al: Acute cholecystitis—Comparison of ultrasound and intravenous cholangiography. Arch Surg 1980 Feb; 115:158-160

12. Sample WF, Sarti DA, Goldstein LI, et al: Gray-scale ultrasonography of the jaundiced patient. Radiology 1978 Sep; 128(3): 719-725

13. Gregg JA, McDonald DG: Endoscopic retrograde cholangiopancreatography and gray-scale abdominal ultrasound in the diagnosis of jaundice. Am J Surg 1979 May; 137:611-615

14. Goldberg HI, Filly RA, Korobkin M, et al: Capability of CT body scanning and ultrasonography to demonstrate the status of the biliary ductal system in patients with jaundice. Radiology 1978 Dec; 129:731-737

15. Weissmann HS, Frank M, Rosenblatt R, et al: Cholescintigraphy, ultrasonography and computerized tomography in the evaluation of biliary tract disorders. Semin Nucl Med 1979 Jan; 9:22-35

16. Weissmann HS, Frank MS, Bernstein LH, et al: Rapid and accurate diagnosis of acute cholecystitis with 99mTc-HIDA cholescintigraphy. AJR 1979 Apr; 132:523-528

17. Suarez CA, Block F, Bernstein D, et al: The role of HIDA/PIPIDA scanning in diagnosing cystic duct obstruction. Ann Surg 1980 Apr; 191:391-396

18. Szlabick RE, Catto JA, Fink-Bennett D, et al: Hepatobiliary scanning in the diagnosis of acute cholecystitis. Arch Surg 1980 Apr; 115:540-544

19. Carter RF, Saypol GM: Transabdominal cholangiography. JAMA 1952; 148:253-255

20. Arner O, Hagberg S, Seldinger SI: Percutaneous transhepatic cholangiography: Puncture of dilated and nondilated bile ducts under roentgen television control. Surgery 1962; 52:561-571

21. Okuda K, Tanikawa K, Emura T, et al: Nonsurgical, percutaneous transhepatic cholangiography—Diagnostic significance in medical problems of the liver. Am J Dig Dis 1974 Jan; 19:21-36

22. Elias E, Hamlyn AN, Jain S, et al: A randomized trial of percutaneous transhepatic cholangiography with the Chiba needle versus endoscopic retrograde cholangiography for bile duct visualization in jaundice. Gastroenterology 1976 Sep; 71(3):439-443

23. Juler GL, Conroy RM, Fuelleman RW: Bile leakage following percutaneous transhepatic cholangiography with the Chiba needle. Arch Surg 1977 Aug; 112:954-958

24. Pollock TW, Ring ER, Oleaga JA, et al: Percutaneous decompression of benign and malignant biliary obstruction. Arch Surg 1979 Feb; 114:148-151

25. Hansson JA, Hoevels J, Simert G, et al: Clinical aspects of nonsurgical percutaneous transhepatic bile drainage in obstructive lesions of the extrahepatic bile ducts. Ann Surg 1979 Jan; 189: 58-61

26. Hoevels J, Ihse I: Percutaneous transhepatic insertion of a permanent endoprosthesis in obstructive lesions of the extrahepatic bile ducts. Gastrointest Radiol 1979 Nov 15; 4(4):367-377

27. Pereiras RV Jr, Rheingold OJ, Hutson D, et al: Relief of malignant obstructive jaundice by percutaneous insertion of a permanent prosthesis in the biliary tree. Ann Intern Med 1978 Nov; 89(5 Pt 1):589-593

28. Molnar W, Stockum AE: Transhepatic dilatation of choledochoenterostomy strictures. Radiology 1978 Oct; 129:59-64

29. Ferrucci JT Jr, Mueller PR, Harbin WP: Percutaneous transhepatic biliary drainage—Technique, results and applications. Radiology 1980 Apr; 135:1-13

30. Ring EJ, Oleaga JA, Freiman DB, et al: Therapeutic applications of catheter cholangiography. Radiology 1978 Aug; 128(2): 333-338

31. Nakayama T, Ikeda A, Okuda K: Percutaneous transhepatic drainage of the biliary tract: Technique and results in 104 cases. Gastroenterology 1978 Mar; 74:554-559

32. McCune WS, Shorb PE, Moscovitz H: Endoscopic cannulation of the ampulla of Vater: A preliminary report. Ann Surg 1968; 167:752-756

33. Oi I, Takemoto T, Kondo T: Fiberduodenoscope—Direct observations of the papilla of Vater. Endoscopy 1969; 1:101-103

34. Davis JL, Milligan FD, Cameron JL: Septic complications following endoscopic retrograde cholangiopancreatography. Surg Gynecol Obstet 1975 Mar; 140:365-367

35. Bilbao MK, Dotter CT, Lee TG: Complications of endoscopic retrograde cholangiopancreatography (ERCP)—A study of 10,000 cases. Gastroenterology 1976 Mar; 70:341-320

36. Cotton PB: ERCP—Progress report. Gut 1977 Apr; 18:316-341

37. Silvis SE, Rohrmann CA, Vennes JA: Diagnostic accuracy of endoscopic retrograde cholangiopancreatography in hepatic, biliary, and pancreatic malignancy. Ann Intern Med 1976 Apr; 84:438-440

38. Cooperman M, Ferrara JJ, Carey LC: Endoscopic retrograde cholangiopancreatography—Its use in the evaluation of nonjaundiced patients with the postcholecystectomy syndrome. Arch Surg 1981; 116:606-609

39. Kawai K, Akasaka Y, Murakami K: Endoscopic sphincterotomy of the ampulla of Vater. Gastrointest Endosc 1974 May; 20:148-151

40. Classen M, Demling L: Endoskopische Sphinkterotomie der Papilla Vateri und Steinextraktion aus dem Ductus choledochus. Dtsch Med Wochenschr 1974 Mar; 99:496-497

41. Siegel JH: Endoscopic management of choledocholithiasis and papillary stenosis. Surg Gynecol Obstet 1979 May; 148:747-752

42. Allen B, Shapiro H, Way LW: Management of recurrent and residual common duct stones. Am J Surg 1981; 142:41-47

43. Safrany L: Transduodenal endoscopic sphincterotomy and extraction of bile duct stones. World J Surg 1978 Jul; 2:457-464

44. Reiter JJ, Bayer HP, Mennicken C, et al: Results of endoscopic papillotomy: A collective experience from nine endoscopic centers in West Germany. World J Surg 1978 Jul; 2:505-511

45. McIver MA: An instrument for visualizing the interior of the common duct at operation. Surgery 1941; 9:112-114

46. Shore JM, Lippman HN: A flexible choledochoscope. Lancet 1965; 1:1200

47. Ashby BS: Choledochoscopy. Clin Gastroenterol 1978 Sep; 7(3):685-700

48. Schein CJ: Influence of choledochoscopy on the choice of surgical procedure. Am J Surg 1975 Jul; 130:74-77

49. Nora PF, Berci G, Dorazio RA: Operative choledochoscopy —Results of a prospective study in several institutions. Am J Surg 1977 Jan; 133:105-110

50. Rattner DW, Warshaw AL: Impact of choledochoscopy on the management of choledocholithiasis—Experience with 499 common duct explorations at the Massachusetts General Hospital. Ann Surg 1981; 194:76-79

51. Okabe N, Kawai K, Kondo O, et al: Operative and postoperative choledochofiberoscopy. Am J Surg 1979 Jun; 137(6): 816-820

52. Moss JP, Whelan JG Jr, Dedman TC III: Postoperative choledochoscopy through the T-tube tract. Surg Gynecol Obstet 1980; 151:806-809

53. Bauer JJ, Salky BA, Gelernt IM, et al: Experience with the flexible fiberoptic choledochoscope. Ann Surg 1981; 194:161-166

54. Schein CJ, Beneventano TC: Biliary manometry: Its role in clinical surgery. Surgery 1970 Feb; 67:255-260

55. Hopton D, White TT: An evaluation of manometric operative cholangiography in 100 patients with biliary disease. Surg Gynecol Obstet 1971 Dec; 133:949-954

56. White TT, Bordley J IV: One percent incidence of recurrent gallstones six to eight years after manometric cholangiography. Ann Surg 1978 Oct; 188(4):562-569

57. McCarthy JD: Radiomanometric guides to common bile duct exploration. Am J Surg 1977 Dec; 134(6):697-701

58. Allen BL, Deveney CW, Way LW: Chemical dissolution of bile duct stones. World J Surg 1978 Jul; 2(4):429-437

59. Mazzariello RM: A fourteen-year experience with nonoperative instrument extraction of retained bile duct stones. World J Surg 1978 Jul; 2(4):447-455

60. Burhenne HJ: Nonoperative instrument extraction of retained bile duct stones. World J Surg 1978 Jul; 2(4):439-445

61. Orloff MJ: Importance of surgical technique in the prevention of retained and recurrent bile duct stones. World J Surg 1978 Jul; 2(4)403-410

62. Dayton MT, Traverso W, Longmire YP Jr: Efficacy of the gallbladder for drainage in biliary obstruction. Arch Surg 1980; 115:1086-1089

63. Jones SA, Smith LL: A reappraisal of sphincteroplasty (not sphincterotomy). Surgery 1972 Apr; 71:565-575

64. Heimbach DM, White TT: Immediate and long-term effects of instrumental dilation of the sphincter of Oddi. Surg Gynecol Obstet 1979 Jan; 148:79-80

65. Smith R, in discussion of, White TT: Indications for sphincteroplasty as opposed to choledochoduodenostomy. Am J Surg 1973; 126:165-170

66. Thomas CG Jr, Nicholson CP, Owen J: Effectiveness of choledochoduodenostomy and transduodenal sphincterotomy in the treatment of benign obstruction of the common duct. Ann Surg 1971 Jun; 173:845-856

67. Stuart M, Hoerr SO: Late results of side to side choledochoduodenostomy and of transduodenal sphincterotomy for benign disorders—A twenty year comparative study. Am J Surg 1972 Jan; 123:67-72

68. Longmire WP: The diverse causes of biliary obstruction and their remedies. Curr Probl Surg 1977 Jun; 14:1-59

69. White TT: Indications for sphincteroplasty as opposed to choledochoduodenostomy. Am J Surg 1973; 126:165-170

70. Hermann R: A plea for safer technique for cholecystectomy. Surgery 1976; 79:609-611

71. Cameron JL, Gayler BW, Zuidema GD: The use of silastic stents in benign and malignant biliary strictures. Ann Surg 1978 Oct; 188:552-561

72. Praderi RC: Twelve years' experience with transhepatic intubation. Ann Surg 1974 Jun; 179:937-940

73. Saypol GM, Kurian G: A technique of repair of stricture of the bile duct. Surg Gynecol Obstet 1969 May; 128:1071-1076

74. Smith R: Hepaticojejunostomy with transhepatic intubation. Br J Surg 1964; 51:186-194

75. Hart MJ, White TT: Central hepatic resection and anastomosis for stricture or carcinoma at the hepatic bifurcation. Ann Surg 1980; 192:299-305

76. Bismuth H, Corlette MB: Intrahepatic cholangioenteric anastomosis in carcinoma at the hilus of the liver. Surg Gynecol Obstet 1975 Feb; 140:170-178

77. Keighley MRB, Lister DM, Jacobs SI, et al: Hazards of surgical treatment due to microorganisms in the bile. Surgery 1974 Apr; 75:578-583

78. Elliott D: Prevention of sepsis in biliary surgery, *In* Controversies in Surgical Sepsis. New York, Praeger, 1980, pp 285-291

79. Chetlin SH, Elliott DW: Preoperative antibiotics in biliary surgery. Arch Surg 1973 Aug; 107:319-323

80. Papachristodoulou AJ, Mackenzie A, Norman J: Single dose cephalosporin prophylaxis in major abdominal surgery, *In* Current Chemotherapy, Vol 2. Zurich, Proceedings of International Symposium on Chemotherapy, 1981, p 856

81. Stone HH, Hooper CA, Kolb LD, et al: Antibiotic prophylaxis in gastric, biliary and colonic surgery. Ann Surg 1976 Oct; 184(4):443:452

82. Keighley MRB, Baddeley RM, Burdon DW: A controlled trial of parenteral prophylactic gentamicin therapy in biliary surgery. Br J Surg 1975 Apr; 62:275-279

83. Polk HC Jr, Lopez-Mayor JF: Postoperative wound infection: A prospective study of determinant factors and prevention. Surgery 1969 Jul; 66:97-103

84. Danzi JT, Makipour H, Farmer RG: Primary sclerosing cholangitis—A report of nine cases in clinic review. Am J Gastroenterol 1976 Feb; 65:109-116

85. Fee HJ, Gewirtz H, Schiller J, et al: Sclerosing cholangitis and primary biliary cirrhosis—A disease spectrum? Ann Surg 1977 Nov; 186(5):589-593

86. Schwartz SI: Primary sclerosing cholangitis: A disease revisited. Surg Clin North Am 1973 Oct; 53:1161-1167

87. Douglass HO Jr: Idiopathic sclerosing cholangitis—Pathophysiologic observations. Am J Surg 1975 Jul; 130:82-87

88. Wiesner RH, LaRusso NF: Clinicopathologic features of the syndrome of primary sclerosing cholangitis. Gastroenterology 1980 Aug; 79:200-206

89. Warren KW, Athanassiades S, Monge JI: Primary sclerosing cholangitis—A study of forty-two cases. Am J Surg 1966 Jan; 111: 23-38

90. Chapman RW, Arborgh BM, Rhodes JM: Primary sclerosing cholangitis: Review of clinical, cholangiographic and hepatic histological features. Gut 1979; 20(10):A954-A955

91. Smallwood RA, Williams HA, Rosenoer VM, et al: Liver-copper levels in liver disease: Studies using neutron activation analysis. Lancet 1968 Dec 21; 2:1310-1313

92. Schoenfield L: Sclerosing cholangitis, *In* Disease of the Gallbladder and Biliary System. New York, John Wiley & Sons, 1977, pp 330-335

93. Dickson ER, Fleming CR, Ludwig J: Primary biliary cirrhosis, *In* Popper H, Schattner F (Eds): Progress in Liver Diseases, Vol 6. New York, Grune & Stratton, 1979, pp 487-502

94. Fraumeni JF Jr: Cancers of the pancreas and biliary tract: Epidemiological considerations. Cancer Res 1975 Nov; 35(II Pt. 2):3437-3446

95. Inouye AA, Whelan TJ Jr: Carcinoma of the extrahepatic bile ducts—A ten year experience in Hawaii. Am J Surg 1978 Jul; 136:90-95

96. Aldrete JS: Malignant neoplasms of the extrahepatic bile ducts. Am Surg 1971 Oct; 38:613-621

97. Whipple AO, Parsons WB, Mullins CR: Treatment of carcinoma of the ampulla of Vater. Ann Surg 1935; 102:763

98. Warren KW, Mountain JC, Lloyd-Jones W: Malignant tumors of the bile-ducts. Br J Surg 1972 Jul; 59:501-505

99. Andersson A, Bergdahl L, van der Linden W: Malignant tumors of the extrahepatic bile ducts. Surgery 1977 Feb; 81:198-202

100. Black K, Hanna SS, Langer B, et al: Management of carcinoma of the extrahepatic bile ducts. Can J Surg 1978 Nov; 21: 542-545

101. Tompkins RK, Thomas D, Wile A: Prognostic factors in bile duct carcinoma—Analysis of 96 cases. Ann Surg 1981 Oct; 194:447-457

102. Thorbjarnarson B: Carcinoma of the bile ducts. Cancer 1959; 12:708-713

103. Klatskin G: Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis. Am J Med 1965; 38:241-256

104. Whelton MJ, Petrelli M, George P, et al: Carcinoma at the junction of the main hepatic ducts. Quart J Med 1969 Apr; 38: 211-229

105. Terblanche J: Is carcinoma of the main hepatic duct junction an indication for liver transplantation or palliative surgery?—A plea for the U tube palliative procedure. Surgery 1976 Feb; 79: 127-128

106. Iwasaki Y, Ohto M, Todoroki T, et al: Treatment of carcinoma of the biliary system. Surg Gynecol Obstet 1977 Feb; 144: 219-224

107. Akwari OE, Kelly KA: Surgical treatment of adenocarcinoma—Location: Junction of the right, left and common hepatic biliary ducts. Arch Surg 1979 Jan; 114:22-25

108. Corlette MB Jr, Bookwalter JR: Individualization of treatment for hilar bile duct cancers. Cancer 1980 Jul 15; 46(2):415-419

109. Tsuzuki T, Uekusa M: Carcinoma of the proximal bile ducts. Surg Gynecol Obstet 1978 Jun; 146:933-943

110. McDermott WV, Peinert RA: Carcinoma in the supraampullary portion of the bile ducts. Surg Gynecol Obstet 1979 Nov; 149(5):681-686

111. Kopelson G, Harisiadis L, Tretter P, et al: The role of radiation therapy in cancer of the extra-hepatic biliary system: An analysis of thirteen patients and a review of the literature of the effectiveness of surgery, chemotherapy and radiotherapy. Int J Radiat Oncol Biol Phys 1977 Sep-Oct; 2:883-894

112. Pilepich MV, Lambert PM: Radiotherapy of carcinoma of the extrahepatic biliary system. Radiology 1978 Jun; 127:767-770

113. Hanna SS, Rider WD: Carcinoma of the gallbladder or extrahepatic bile ducts: The role of radiotherapy. Can Med Assoc J 1978 Jan 7; 118:59-61

114. Mackie CR, Cooper MJ, Lewis MH, et al: Non-operative differentiation between pancreatic cancer and chronic pancreatitis. Ann Surg 1979 Apr; 189:480-487

115. Moossa AR, Levin B: The diagnosis of "early" pancreatic cancer: The University of Chicago experience. Cancer 1981; 47: 1688-1697

116. Go VLW, Taylor WF, Dimagno EP: Efforts at early diagnosis of pancreatic cancer: The Mayo clinic experience. Cancer 1981; 47:1698-1703

117. Morgan RG, Wormsley KG: Progress report—Cancer of the pancreas. Gut 1977 Jul; 18:580-592

118. Gross R: The Surgery of Infancy and Childhood. Philadelphia, WB Saunders, 1953

119. Kasai M, Watanabe I, Ohi R: Follow-up studies of long-term survivors after hepatic portoenterostomy for "noncorrectable" biliary atresia. J Pediatr Surg 1975 Apr; 10:173-182

120. Landing BH: A changing approach to neonatal hepatitis and biliary atresia (Editorial). Pediatrics 1974 May; 53:647-648

121. Lilly JR: The Japanese operation for biliary atresia—Remedy or mischief? Pediatrics 1975 Jan; 55:12-22

122. Miyata M, Satani M, Ueda T, et al: Long-term results of hepatic portoenterostomy for biliary atresia—Special reference to postoperative portal hypertension. Surgery 1974 Aug; 76:234-237

123. Flanigan PD: Biliary cysts. Ann Surg 1975 Nov; 182(5): 635-643

124. Caroli J: Diseases of the intrahepatic biliary tree. Clin Gastroenterol 1973; 2:147-161

125. Watts DR, Lorenzo JA, Beal JM: Proceedings: Congenital dilatation of the intrahepatic biliary ducts. Arch Surg 1974 Apr; 108:592-598

126. Lilly JR: The surgical treatment of choledochal cyst. Surg Gynecol Obstet 1979 Jul; 149:36-42

127. McClelland RN: Controversy about the surgical treatment of choledochal cysts (Editorial). Gastroenterology 1978 Jun; 74: 1336-1337

128. Glenn F, McSherry CK: Congenital segmental cystic dilatation of the biliary ductal system. Ann Surg 1973 Jun; 177:705-713

129. Filler RM, Stringel G: Treatment of choledochal cyst by excision. J Pediatr Surg 1980; 15:437-443

130. Kasai M, Asakura Y, Taira Y: Surgical treatment of choledochal cyst. Ann Surg 1970 Nov; 172:844-851

Specialty Conference

Participants
MARTIN T. STEIN, MD
STEPHEN A. SPECTOR, MD
NANCY OLMSTED, MD
PAUL THOMBS, MD

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Refer to: Stein MT, Spector SA, Olmsted N, et al: Chronic cough in infants younger than three months—University Hospital, San Diego, University of California, San Diego (Specialty Conference). West J Med 1982 Jun; 136: 505-512

Chronic Cough in Infants Younger Than Three Months

MARTIN T. STEIN, MD:* The subject of this conference is the diagnostic problem posed by very young infants with a chronic cough. As pediatricians we are aware that an infant with a pulmonary infection may have no cough. When an infant has a persistent cough, a careful workup is warranted. The case will be presented by Dr. Thombs.

Case Presentation

PAUL THOMBS, MD:† The patient is a two-month-old Mexican female infant who was seen with a one-month history of rhinorrhea and cough associated with intermittent mild to moderate respiratory distress. She was born weighing 3.2 kg (7 lbs) following a full-term gestation that was complicated by uterine bleeding at three, five and seven months. The infant's 27-year-old mother was gravida 5, para 3, abortus 2. Labor and delivery occurred without complications and the perinatal period was uneventful. She did well during the first month and gained weight appropriately on breast milk supplemented with a modified cow's milk formula with iron. At five weeks of age she became tachypneic; intercostal retractions developed as did a cough that was characterized as staccato and periodic. She was examined at a community clinic where a diagnosis of bronchiolitis was made and ampicillin prescribed. During the next three weeks she continued to be intermittently tachypneic and had occasional fever. There was no vomiting, diarrhea or rash. Despite the intermittent tachypnea and respiratory distress, she continued to eat well and gain weight. The day before admission, however, she had a 30- to 60-second episode of apnea and cyanosis and was referred to University Hospital. She had not been exposed to any known infectious diseases, and she had not received any immunizations. There was no familial history of pneumonia or cardiac disease. She lived with two siblings and her parents, all of whom were well.

PHYSICIAN IN THE AUDIENCE: *As a clue to possible cardiac dysfunction, were feedings prolonged or associated with excessive diaphoresis?*

DR. THOMBS: There was no history of sweating and her feedings were of normal duration. On physical examination she had a temperature of 37.8°C (100°F), respirations were 60 per minute with mild intercostal retractions and the pulse rate was 160 per minute. The head circumference was 38 cm, height 60 cm and weight 4.8 kg (10 lbs 9 oz). There was a monilial rash on the perineum. Skin turgor was normal. Examination of the ears, nose and throat showed no abnormalities. There was no conjunctival erythema or discharge. Lymph nodes were not enlarged. On observing her respiratory pattern, we did not note grunting respirations or flaring of the nostrils. On auscultation of the chest, scattered inspiratory rales were heard in the right axilla. Precordial activity was quiet and there was no murmur heard. Pulses were equal and normal in strength. The abdomen was soft and nontender. The liver was palpable 2 to 3 cm below the right costal margin; a tip of the spleen was palpable. Neurologic, genitourinary and extremity examinations showed no abnor-

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ABBREVIATIONS USED IN TEXT

CF = complement fixation
CFC = cystic fibrosis center
CMV = cytomegalovirus
RSV = respiratory syncytial virus

malities. Her development was appropriate for her age.

PHYSICIAN IN THE AUDIENCE: *Can you describe the child's cough?*

DR. THOMBS: It was periodic and staccato.

PHYSICIAN IN THE AUDIENCE: *Did this child ever wheeze?*

DR. THOMBS: Wheezing was not noted by the referring physician or on admission to hospital.

PHYSICIAN IN THE AUDIENCE: *Did she ever vomit before a coughing episode? This would suggest aspiration due to an anatomic or functional disturbance in the gastrointestinal tract.*

DR. THOMBS: No.

PHYSICIAN IN THE AUDIENCE: *Was cyanosis associated with the coughing spells?*

DR. THOMBS: Not on the occasions that were witnessed.

DR. STEIN: Would those in the audience like to suggest a differential diagnosis? . . . [*The physicians at the conference generated the following list of diagnostic considerations in this thriving two-month-old infant with a chronic cough, intermittent respiratory distress and rales.*] (See Table 1).

The initial x-ray studies of the chest (Figure 1) are valuable in excluding several of the diagnoses considered likely on the basis of the history and physical examination. The congenital defects of the parenchyma of the lung were not consistent with a diffuse, symmetrical increase in peribronchial markings. The structural anomalies produce focal radiodensities or lucencies. In a similar fashion, recurrent pulmonary infections associated with a compromised immune system or recurrent aspiration due to tracheoesophageal fistula or gastroesophageal reflux usually produce large patchy areas of pneumonia. The findings on the chest x-ray film excluded the possibility of a diaphragmatic hernia in which there is bowel gas in the chest or displacement of lung and mediastinum.

The pertussis syndrome is a form of tracheobronchitis in which the lungs are usually minimally involved; at other times, a child with pertussis may have a perihilar infiltrate that produces a "shaggy heart border" appearance. Occasionally pertussis may be associated with a significant pneumonic process. The findings on this child's

Figure 1.—Photographs of roentgenograms of the chest, posteroanterior **(left)** and lateral **(right)** views. There was a general increase in radiolucency consistent with all the features of hyperinflation, along with a streaky increase in markings radiating out from the hilum.

TABLE 1.—*Differential Diagnosis*

Pneumonia
Adenovirus
Respiratory syncytial virus
Chlamydia
Mycoplasma
Wilson-Mikity syndrome
Bronchopulmonary dysplasia
Pertussis
Tracheoesophageal fistula (H type) with aspiration
Vascular ring with aspiration
Gastroesophageal reflux with aspiration
Immunodeficiency with recurrent respiratory infection
Hypersensitivity reaction (for example, infantile asthma)
Congenital anatomic pulmonary defect
Lung cyst versus bronchial cyst
Congenital emphysema
Sequestered lobe
Cystic adenomatosis
Bronchial stenosis, web or atresia
Diaphragmatic hernia
Tuberculosis
Foreign body in airway or esophagus
α-1-Antitrypsin deficiency
Congenital rubella or cytomegalovirus
Congestive heart failure

chest radiograph are not typical for pertussis but they certainly do not rule out that consideration.

The Wilson-Mikity syndrome is a form of pulmonary dysmaturity that produces respiratory symptoms a few weeks after birth. However, it develops in premature babies, especially those below 1,500 grams. Furthermore, the chest roentgenogram findings in Wilson-Mikity syndrome are considerably different from those in our patient. Infants with the Wilson-Mikity syndrome have coarse pulmonary infiltrates with a lacy configuration in association with hyperlucent foci.

The chest radiograph findings in this infant have all the features of pneumonitis. Hyperinflation and a diffuse, symmetrical increase in bronchial markings are associated with many viral forms of pneumonia and chlamydial pneumonitis in early infancy. A bacterial cause characteristically would be associated with a lobular pattern of pneumonia without substantial distal air trapping. The absence of hilar adenopathy, focal infiltrates or pleural effusion is against pulmonary tuberculosis.

As is the custom at this conference, we will now ask physicians in the audience to request specific laboratory tests from Dr. Thombs in an order that is both rational and cost conscious for establishing a diagnosis. Dr. Thombs will summarize his answers to these questions which, during the conference, were answered individually.

DR. THOMBS: Laboratory values were as follows: the admission hemoglobin was 9.8 grams per dl and hematocrit 31 percent; red blood cell indices were normal for age. The leukocyte count was 20,000 per cu mm with 21 percent polymorphonuclear cells, 4 percent band forms, 65 percent mature lymphocytes, 7 percent monocytes and 3 percent eosinophils. There were no atypical lymphocytes on the peripheral blood smear. Platelet count, urinalysis and serum electrolyte values were normal. A tuberculin test was negative at 48 hours. An arterial blood gas analysis in room air gave the following results: pH, 7.34; carbon dioxide partial pressure (P_{CO_2}), 35 mm of mercury, and oxygen pressure (P_{O_2}), 54 mm of mercury. A specimen obtained by nasopharyngeal swab for fluorescent antibody staining with pertussis antibody gave negative results. A culture of nasopharyngeal secretions was also negative for pertussis. The viral laboratory was unable to identify respiratory syncytial virus (RSV) or any other viral agent from a nasopharyngeal specimen. Cultures for *Chlamydia* were negative. Serum immunoglobulin (IgG, IgA, IgM) studies were normal for age. Cold agglutinin and mycoplasma titers were negative.

Following admission, her respiratory distress increased moderately, but the infant responded to hydration, mist tent therapy and physical therapy of the chest. Over the next 16 hours her temperature returned to normal and she looked well. She was discharged after five days without tachypnea and only a rare cough. We assumed she had a viral pneumonia and arrangements were established for follow-up in the Primary Care Clinic. However, she was readmitted five days later after a 24-hour period of episodic cough, tachypnea and facial petechiae. Her appearance on physical examination was similar to that at the time of the first admission. At this time a sweat chloride determination showed 85 mEq per liter of chloride. Of interest, a urine culture sent to the virology laboratory at the time of the first admission yielded cytomegalovirus (CMV).

Discussion

STEPHEN A. SPECTOR, MD:* When seen this two-month-old infant had a one-month history of rhinorrhea and cough associated with a low-grade

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fever. An episode of apnea and cyanosis occurred on the day before her admission to hospital. On admission, her chest x-ray films showed diffuse, symmetrically increased perihilar markings associated with mild hyperinflation. This clinical presentation is most often seen with infection by respiratory viruses, *Chlamydia* or pertussis. Recently, *Pneumocystis carinii* has been implicated as a possible causal agent in pneumonitis in young immunocompetent infants. Mycoplasma or tuberculosis are less often identified. Several features in this patient made many of these potential diagnoses unlikely.

The subacute course of the infant's illness suggested that an acute bacterial pathogen (that is, *Hemophilus influenzae, Streptococcus pneumoniae* or *Staphylococcus aureus)* was extremely unlikely. Tuberculosis in infancy frequently shows up as miliary disease associated with meningitis. The chest x-ray films in this patient showed no hilar adenopathy and there was no evidence of a miliary or consolidative pattern that would suggest tuberculosis. Although *Mycobacterium tuberculosis* is endemic in Mexico, there was no family history of tuberculosis. We have found purified protein derivative (PPD) skin testing of family members of infants with suspected tuberculosis to be extremely helpful in establishing the diagnosis in babies who frequently themselves have negative tuberculin skin tests. The diagnosis of tuberculosis in an infant such as this, however, would be unlikely.

Mycoplasma pneumoniae infections may occur in infancy, but usually do not result in pneumonia until approximately five to nine years of age.[1] The *Mycoplasma* titer in this infant was less than 1:8 late in the course of her infection. Pertussis caused by *Bordetella pertussis* or *Bordetella parapertussis* classically begins after seven to ten days of a catarrhal stage characterized by nonspecific systemic and respiratory symptoms. Coughing begins sporadically and worsens over one to two weeks to a paroxysmal stage when the whoop (a forced inspiration over a partially closed glottis) may be observed. Lymphocytosis frequently occurs during this period. Infants under six months of age may have coughing without whooping and apneic spells may develop. Chest x-ray films in mild cases may show perihilar infiltration. In more severe cases, atelectasis or mediastinal emphysema may be seen. Secondary bacterial pneumonia leads to lobar consolidation. The cultures of nasopharyngeal secretions of this infant, however, which were placed directly onto Bordet-Gengou agar, as well as fluorescent antibody staining for *B pertussis* and *B parapertussis,* were negative, making the diagnosis of pertussis unlikely.

Evidence of *Chlamydia trachomatis* may be found in as many as 73 percent of infants less than six months old with afebrile pneumonia and it is the sole pathogen in approximately 40 percent of infants with diffuse interstitial pneumonia.[2] Only 50 percent of children who develop chlamydial pneumonia have a history of conjunctivitis.[3] A low-grade or absent fever associated with a staccato cough is characteristic of the infection. An absolute eosinophilia is frequently present, associated with elevated levels of serum immunoglobulins IgM, IgG and IgA.[4] These infections can cause prolonged pneumonia. Although chlamydia would have been a likely diagnosis in this child, the culture for *C trachomatis* was negative and her titer to *Chlamydia* was less than 1:8.

Viral infections should always be considered in infants with diffuse interstitial pneumonia and cough. Dr. James Connor[5] first described the association of adenovirus with a pertussislike syndrome. Recent studies have suggested that adenovirus pertussis most frequently occurs concomitantly with the presence of *B pertussis,* though adenovirus may cause similar symptoms as the sole infecting agent.[6,7] Adenoviral infections may occur with acute fulminant disease, particularly in patients with compromised pulmonary function. In addition, adenovirus infection may contribute to the development of bronchiectasis in certain children.[8] Enteroviruses, though frequently not considered as respiratory pathogens, can cause "pure" respiratory tract disease in infancy. Parainfluenzal viruses are the second most common virus identified in infants with pneumonia, accounting for 10 percent of lower respiratory tract disease. The most common respiratory tract virus causing pneumonia in infancy is respiratory syncytial virus, which may be identified in from 10 percent to 25 percent of children with pneumonia.[9] These infections are frequently associated with low-grade fever, diffuse interstitial pneumonia and cough. In addition, as many as 20 percent of infants less than six months old can experience periods of apnea with RSV infection.[10] This is particularly prevalent in premature infants, but may occur in full-term babies as well. Although RSV is a common causal agent in pneumonia of young infants, in this case the cultures were negative for

the virus and her RSV-complement fixation (CF) titer remained less than 1:8.

Cytomegalovirus was identified in the patient's urine specimen at five weeks of age. The infant's CMV-CF titer was 1:32 at 12 and 15 weeks old, while her mother's CMV-CF titer was 1:64. The association of CMV with this infant's pneumonia is unclear. Pulmonary disease occurs in infants who are congenitally infected with CMV, but is more common with acquired infection in children and adults.[11,12] Immunocompromised individuals and particularly patients who have had bone marrow transplantation are at high risk of having severe and frequently fatal CMV pneumonia develop.[13,14] Protracted CMV pneumonitis has been described in full-term infants[15] and frequently occurs with CMV acquired by premature infants in intensive care nurseries.[16,17] The sequelae of CMV pneumonia in infants with cystic fibrosis are unknown.

It is difficult at three months of age to determine whether an infant was congenitally infected with CMV. Less than 5 percent of these babies congenitally infected with CMV will show clinical evidence of disease. It is quite possible that this infant acquired her infection postnatally. From 3 percent to 25 percent of women harbor CMV in their cervices, and 25 percent of infants passing through a cervix so infected acquire infection with virus.[18] In addition, breast milk may be a source of CMV in infants because 20 percent to 50 percent of seropositive women excrete CMV in their milk.[19,20] The incidence of CMV dramatically increases in lower socioeconomic groups and in underdeveloped countries. It is likely, therefore, that this infant acquired her infection postnatally. In this regard I feel that an acquired CMV infection developed in this infant superimposed on her underlying disease, cystic fibrosis. Her clinical course of protracted pneumonia was sufficiently atypical to mandate that a sweat test be done. Although several microbial agents may be responsible for protracted respiratory disease in infancy, any of these diseases may occur with cystic fibrosis. A sweat test should always be included in the evaluation of such a condition.

Cystic Fibrosis

NANCY OLMSTED, MD:* Infants with cystic fibrosis may become severely ill with respiratory distress at a few months of age. The clinical course varies. Wheezing, a paroxysmal cough, recurrent pneumonia or an apparent bronchiolitis may develop, with hyperinflation, cyanosis and respiratory distress that does not clear rapidly. Other infants with cystic fibrosis have less respiratory distress with only minimal coughing or wheezing. Those with the most severe compromise of their small terminal airways require early and appropriate medical care. Some of these are not diagnosed until autopsy and are thought clinically to have had asthma or bronchiolitis. Radiographs may reveal extensive hyperinflation but are often read as normal or as representative of a baby who takes a big breath. The radiographs of other infants with cystic fibrosis show infiltrates that suggest a viral pneumonia process. Diagnosis may be missed in these sick infants if they do not receive the benefit of an accurate pilocarpine iontophoresis sweat test. In a classic review of severe respiratory tract disease in infants with cystic fibrosis, Lloyd-Still and associates[21] noted that the average time of diagnosis after onset of illness was six weeks and 60 percent of these died of the disease.

The outlook is much brighter when infants with cystic fibrosis are diagnosed early and given prolonged aggressive treatment with extensive chest physical therapy and intensive intravenous administration of antibiotic medications. The underlying lesion in the disease is a combination of obstruction and infection of the terminal bronchioles. Although virus (for example, respiratory syncytial virus or adenovirus) may be the precipitating cause of the acute infection, bacterial pathogens rapidly invade the airways. These include a wide variety of organisms such as *S aureus, H influenzae, Klebsiella, Proteus, Pseudomonas* and other Gram-negative organisms. In our experience in San Diego, *Pseudomonas* and *Klebsiella* have been the predominant organisms. Depending on the severity of the disease, a course of therapy is prescribed for several weeks with the appropriate antibiotic drugs determined by culture and sensitivity testing of tracheal secretions. Other infants require a more prolonged period of hospital care. Alternatively, appropriate antibiotic therapy administered orally and chest physical therapy given at home between hospital admissions benefit some youngsters.

Although many infants with cystic fibrosis have severe wheezing, bronchodilators, including both theophylline and β-adrenergic agents, are only partially effective. Furthermore, side effects of high doses of theophylline may interfere with good

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nutrition. In occasional patients steroid medications are helpful, but they should be used only with appropriate antibiotic coverage and when the infection is at least partially under control. In addition, a child must be maintained in sound nutritional status with supplementation with enzymes if needed and appropriate protein, calories and vitamins.

Some of these patients with cystic fibrosis who were diagnosed early at University Hospital have been severely ill with marked hypoxemia and hypercarbia and have required protracted stay in hospital for several months. All of these patients recovered gradually over the next couple of years, and among those followed to six or seven years of age, normal findings on chest radiographs and pulmonary function tests have been recorded. However, infants with cystic fibrosis accompanied by a severe bronchiolitis-bronchiectasis pattern who had not received aggressive therapy until after an appropriate referral at age 15 to 24 months did not recover, all of them dying within 6 to 12 months.

The diagnosis of cystic fibrosis should be made as early as possible when there are clinical features of bronchiolitis, and treatment should be aggressively administered.

PHYSICIAN IN THE AUDIENCE: *What is the long-term course of cystic fibrosis when it is diagnosed early, as in the present case?*

DR. OLMSTED: Over the years there has been pronounced improvement in the survival figures of patients with cystic fibrosis. The current median survival is 20 years of age. Of course, the disease is variable and some patients are living into their 30's and 40's. The notable improvement in survival in patients with cystic fibrosis has been accompanied by a dramatic reduction in the number of deaths in the first few years of life.

Early diagnosis of patients with cystic fibrosis has been shown to be important. Affected siblings of known patients with cystic fibrosis, who were diagnosed very early on the basis of the known autosomal recessive pattern of inheritance, had better results on pulmonary function studies and fewer hospital admissions than their brothers or sisters who were diagnosed at a later, symptomatic stage.

Patients with cystic fibrosis diagnosed early represent a mixed population; some with minimal disease are diagnosed by an alert physician, whereas in others a more severe initial course suggests the need for diagnostic sweat chloride determination. The ultimate prognosis for any infant cannot be made at the time of diagnosis. If there is improvement over the course of a year with return of the chest x-ray findings to near normal and the patient continues to receive aggressive therapy at a cystic fibrosis center (CFC), the prognosis may be as good as that of the healthiest patients with cystic fibrosis. If an infant's condition does not improve during one year or shows deterioration, the prognosis is poor.

PHYSICIAN IN THE AUDIENCE: *What about cystic fibrosis patients who are undiagnosed and untreated?*

DR. OLMSTED: About 80 percent of patients seen in cystic fibrosis centers are diagnosed in the first

TABLE 2.—*Chest Radiography Findings in Evaluation of Chronic Cough in Infants Under Three Months*

Normal		*Abnormal*			
				Consolidations	
Wheezing	*No Wheezing*	*Cardiomegaly*	*Hyperinflation*	*Lobar*	*Bronchopneumonia*
Asthma	Upper respiratory tract infection	Congenital heart disease	Bronchiolitis	Bacterial pneumonia	Cystic fibrosis
Anomalous great vessels	Tracheobronchitis due to	Congenital anemias	Asthma	Viral pneumonia	Pneumonia
Aspiration	Pertussis		Cystic fibrosis	*Mycobacterium tuberculosis*	Viral
Cystic fibrosis	Parapertussis		Pneumonia	"Pseudoconsolidation"	Bacterial
	Adenovirus		Chlamydial	Eventration of diaphragm	Chlamydial
	Environmental agents		Respiratory syncytial virus	Diaphragmatic hernia	Aspiration
	Cigarette smoke		Adenovirus	Sequestered lobe	H-type (tracheoesophageal) fistula
	Fumigation		Cytomegalovirus	Bronchogenic cyst	Anomalous great vessel
	Baby powder		Congenital emphysema	Cystic fibrosis	Gastroesophageal reflux
	Cystic fibrosis			Aspiration	Immunodeficiency
					Parasites

year of life. Some of the undiagnosed patients have mild disease and may not be identified until their adolescence or early adulthood. Others die in respiratory failure undiagnosed in the early months of life. This may include a significant number of infants and explains some of the variation in the reported incidence of cystic fibrosis in different populations.

DR. STEIN: Infants under three months of age with a cough of more than a few weeks' duration provide a primary care pediatrician with a diagnostic challenge. As we have seen in this conference, it is important to vigorously pursue a specific causal diagnosis. I have been impressed with the usefulness of using one sign on physical examination—wheezing—and the findings on chest radiograph as a method of classifying these infants and beginning the diagnostic process.

Table 2 is a diagram that begins by separating those infants with normal findings on the chest radiographs from those with abnormal findings. If the x-ray study is normal, the lesion that is producing a cough is either in the upper airway or too small at this stage in development to produce a density. In that case, wheezing, a result of small airway obstruction, provides an important clue to a lower tract obstructive process. The absence of either wheezing or pathologic findings on x-ray examination of the chest suggests an upper respiratory tract inflammatory process such as pertussis or an upper respiratory tract viral infection. Cystic fibrosis always remains a possible diagnosis. Mass lesions of the upper airway are unlikely without notable stridor.

When findings on the chest radiograph are abnormal, attention should be directed to the possibility of cardiomegaly, hyperinflation and consolidations. An enlarged heart in an acyanotic infant usually points to a form of congenital heart disease with a substantial left-to-right shunt; chronic cough suggests left-sided congestive heart failure. A severe form of congenital anemia (for example, isohemagglutinin sensitization or congenital spherocytosis) may present with a chronic cough in early infancy due to high-output congestive heart failure.

Although small airway obstructive disease characteristically produces both wheezing and a hyperinflated chest seen on the radiograph, occasionally wheezing may be absent or only intermittent. In these cases, hyperinflation on x-ray examination of the chest may give an important clue to the pneumonias listed in Table 2 and cystic fibrosis.

Consolidations seen on chest radiographs in infants, as in older patients, rarely provide a clue to a specific diagnosis. While considerable bacterial pneumonia usually produces lobar consolidation and viral pneumonia is associated with streaky bronchopneumonic infiltrates, any infectious agent can produce either radiographic pattern. Furthermore, apparent consolidations of lung parenchyma ("pseudoconsolidation") may represent a congenital structural defect of the lung, airway or diaphragm. Dr. Spector reminded us that as many as 60 percent of pneumonias in the first three months of life may be due to a chlamydial agent. This patient reminds us of the importance of considering other less common, potentially treatable causes.

PHYSICIAN IN THE AUDIENCE: *How unusual is it to discover cystic fibrosis in a Mexican child?*

DR. STEIN: The uncommon occurrence of this disease in nonwhite children undoubtedly dissuaded house staff and attending physicians from obtaining a sweat chloride determination during the initial hospital stay of the Mexican patient presented today. At University Hospital, San Diego, where many children of Mexican heritage are cared for, cystic fibrosis among children of Mexican heritage is not common. Only five Mexican or Mexican-American children with cystic fibrosis have been seen in our pediatric service in the past decade, among over 200 patients with cystic fibrosis cared for by the CFC.

This experience is consistent with the reported incidence of cystic fibrosis. Among white patients the incidence of cystic fibrosis is between 1 in 2,000 to 1 in 3,000 live births, which gives an estimated gene frequency of 3 percent to 5 percent.[22] Among black newborns in Washington, DC, an incidence of 1 in 17,033 live births has been reported.[23] Among Asians, the incidence has been estimated as only 1 in 90,000.[24] I am not aware of a report of the incidence of cystic fibrosis among Mexican children. An oversimplified extrapolation of the Mexican-white ratio in the San Diego CFC (approximately 1:40), along with the incidence of cystic fibrosis in white newborns of 1 in 2,000, would give an incidence in Mexican children of 1 in 80,000. Ethnic differences are consistent with

variable gene frequencies for the carrier state of cystic fibrosis in this autosomal recessive disorder.

Summary

It is not widely recognized that cystic fibrosis presents in infants with all the features of a bronchiolitic condition. This is a serious, potentially fatal, condition. When recognition leads to the establishment of an early diagnosis and the institution of comprehensive aggressive therapy, the prognosis for infants and children can be good.

REFERENCES

1. Foy HM, Kenny GE, Cooney MK, et al: Long-term epidemiology of infections with *Mycoplasma pneumoniae*. J Infect Dis 1979 Jun; 139.681-687

2. Beem MO, Saxon EM: Respiratory-tract colonization and a distinctive pneumonia syndrome in infants infected with *Chlamydia trachomatis*. N Engl J Med 1977 Feb 10; 296:306-310

3. Harrison HR, English MG, Lee CK, et al: *Chlamydia trachomatis* infant pneumonitis: Comparison with matched controls and other infant pneumonitis. N Engl J Med 1978 Mar 30; 298(13): 702-708

4. Tipple MA, Beem MO, Saxon EM: Clinical characteristics of the afebrile pneumonia associated with *Chlamydia trachomatis* infection in infants less than 6 months of age. Pediatrics 1979 Feb; 63:192-197

5. Connor JD: Evidence for an etiologic role of adenoviral infection in pertussis syndrome. N Engl J Med 1970 Aug 20; 283: 390-394

6. Nelson KE, Gavitt F, Batt MD, et al: The role of adenoviruses in the pertussis syndrome. J Pediatr 1975 Mar; 86:335-341

7. Keller MA, Aftandelians R, Connor JD: Etiology of pertussis syndrome. Pediatrics 1980 Jul; 66(1):50-55

8. James AG, Long WR, Liang AY, et al: Adenovirus type 21 bronchopneumonia in infants and young children. J Pediatr 1979 Oct; 95(4):530-533

9. Zollar LM, Krause HE, Mufson MA: Microbiologic studies on young infants with lower respiratory tract disease. Am J Dis Child 1973 Jul; 126:56-60

10. Bruhn FW, Mokrohisky ST, McIntosh K: Apnea associated with respiratory syncytial virus infection in young infants. J Pediatr 1977 Mar; 90:382-386

11. Smith SD, Cho CT, Brahmacupta N, et al: Pulmonary involvement with cytomegalovirus infections in children. Arch Dis Child 1977 Jun; 52:441-446

12. Nankervis GA, Kumar ML: Diseases produced by cytomegaloviruses. Med Clin North Am 1978 Sep; 62:1021-1035

13. Abdallah PS, Mark JBK, Merigan TC: Diagnosis of cytomegalovirus pneumonia in compromised hosts. Am J Med 1976 May 1; 61(3):326-332

14. Myers JD, Spencer HC Jr, Watts JC, et al: Cytomegalovirus pneumonia after human marrow transplantation. Ann Intern Med 1975 Feb; 82:181-188

15. Whitley RJ, Brasfield D, Reynolds DW, et al: Protracted pneumonitis in young infants associated with perinatally acquired cytomegaloviral infection. J Pediatr 1976 Jul; 89:16-22

16. Spector SA, Schmidt K, Ticknor W, et al: Cytomegaloviruria in older infants in intensive care nurseries. J Pediatr 1979 Sep; 95:444-446

17. Ballard RA, Drew WL, Hufnagle KG, et al: Acquired cytomegalovirus infection in preterm infants. Am J Dis Child 1979 May; 133:482-485

18. Kumar ML, Gold E, Nankervis GA: Risk of acquired cytomegalovirus (CMV) infection in infants of maternal CMV excretors. Pediatr Res 1975; 9:512

19. Hayes K, Danks DM, Gibas H, et al: Cytomegalovirus in human milk. N Engl J Med 1972 Jul 27; 287:177-178

20. Stagno S, Reynolds DW, Pass RF, et al: Breast milk and the risk of cytomegalovirus infection. N Engl J Med 1980 May 8; 302:1073-1076

21. Lloyd-Still JD, Kon-Taik K, Schwachman H: Severe respiratory distress in infants with cystic fibrosis. Pediatrics 1974 May; 53:678-682

22. di Sant'Agnese PA, Talamo RC: Pathogenesis and physiopathology of cystic fibrosis of the pancreas—Fibrocystic disease of the pancreas (mucoviscidosis). N Engl J Med 1967 Dec 14; 277: 1287-1294

23. Kulczycki LL, Schauf V: Cystic fibrosis in blacks in Washington, DC. Am J Dis Child 1974 Jan; 127:64-67

24. Ikai K: Cystic fibrosis cases found by re-examination of histology of pancreas and postmortem protocol in Japanese children and sweat tests on siblings. Acta Paediatr Jpn 1965; 7:23

Refer to: Kacich R, Linker C: Thrombotic thrombocytopenic purpura—Medical Staff Conference, University of California, San Francisco. West J Med 1982 Jun; 136:513-520

Thrombotic Thrombocytopenic Purpura

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. NAUGHTON:* *This Medical Staff Conference will be devoted to a topic in hematology. We will begin with a case presentation by Ray Kacich, a medical student at the University of California.*

Case Presentation

MR. KACICH:† The patient, a 55-year-old Chinese woman, was transferred to the University of California, San Francisco (UCSF), Medical Center with a one-week history of petechiae, ecchymoses, intermittent fever and recurrent mental status changes. Two years before admission the patient had noted the onset of easy bruising, and an antifibrinolytic agent to be taken orally was prescribed.

Eleven days before transfer to UCSF, the patient arrived in San Francisco from Hong Kong with symptoms of headache, nausea, fatigue and dizziness. Over the next few days increased bruising developed and she was admitted to a local hospital where her physical examination findings were noteworthy for purpura. Laboratory studies elicited the following values: hematocrit 25 percent (normal, 37 to 48), reticulocyte count 7 percent (normal, 0.5 to 1.5) and platelet count 7,000 per cu mm (normal, 150,000 to 350,000). Coombs' tests, direct and indirect, were negative. The specimen from a bone marrow biopsy showed erythroid hyperplasia. A diagnosis of immune thrombocytopenic purpura with hemolytic anemia was entertained. The patient was discharged on a regimen of prednisone, 80 mg to be taken orally daily.

The morning after discharge, the patient was found in bed curled in a fetal position and talking unintelligibly. She was readmitted to the hospital with a temperature of 37.9°C. Physical examination showed new petechiae but there were no abnormalities on neurologic examination. A computerized tomography (CT) scan of the brain raised a slight suspicion of a left internal capsule lucency. Sensorium cleared spontaneously that evening. The next morning mental status again showed decline, and mild right facial weakness, right upper extremity drift and receptive aphasia were noted. The patient was transferred to UCSF.

On admission to UCSF, she was noted to be lethargic. Her blood pressure was 117/62 mm of mercury, pulse 96 a minute and regular, respirations 18 per minute and temperature 38°C. The

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ABBREVIATIONS USED IN TEXT

CT = computerized tomography
DIC = disseminated intravascular coagulation
HLA = human leukocyte antigen
LDH = lactate dehydrogenase
PAF = platelet-aggregating factor
PAFI = platelet-aggregating factor inhibitor
TTP = thrombotic thrombocytopenic purpura

patient had numerous petechiae and ecchymoses. Examination of head, eyes, ears, nose and throat was normal. The lungs were clear and the cardiovascular system appeared normal. Abdominal tone was increased with left upper quadrant tenderness. There was no organomegaly and bowel sounds were normal. Guaiac test of a stool was negative for occult blood. Neurologically the patient was symmetrically hyperreflexic, with probably decreased strength of the right extremities and an upgoing toe on the left.

Admission laboratory data included a leukocyte count of 12,600 per cu mm, hematocrit 24 percent, reticulocyte count 17 percent and platelet count 13,000 per cu mm. Results of coagulation studies were normal. Coombs' tests, direct and indirect, were negative. A peripheral blood smear showed numerous red cell fragments, nucleated red cells, spherocytes, myelocytes and increased numbers of reticulocytes. Analysis of urine specimen showed 2+ hemoglobin, with 10 to 25 red cells and white cells per high-power field. Chest x-ray films and electrocardiograms were normal. A diagnosis of thrombotic thrombocytopenic purpura (TTP) was made.

On her second hospital day the patient underwent placement of a Scribner shunt concurrent with a 10-unit platelet transfusion, followed by her first of seven plasmaphereses. Aspirin and dipyridamole therapy were begun and steroid doses were tapered. Within 12 hours of the first plasmapheresis the patient's condition was dramatically improved. By the fifth hospital day, after four plasmaphereses, she was asymptomatic and assessed by her family to be totally recovered. The platelet count had risen to 105,000 per cu mm and the peripheral blood smear showed fewer red cell fragments. On the sixth hospital day the patient began to relapse; lethargy and aphasia returned. The platelet count fell to 13,000 per cu mm and platelet transfusions did not raise this count. Plasmapheresis was restarted after a one-day lapse. Aspirin and dipyridamole therapy and heparin infusion into the Scribner shunt were discontinued. The patient also received intravenously methylprednisolone sodium succinate (Solu-Medrol), 1 gram, and vincristine sulfate, 2 mg. Mental status improved after plasmapheresis and the hematocrit, which had fallen 12 percent in the preceding 36 hours, became stable at 23 percent.

The next morning, hospital day 10, the patient had a generalized tonic-clonic seizure. Noncontrast CT scan of the head was normal, and she underwent her seventh plasmapheresis. After the procedure, the patient became hypotensive and was transferred to the Coronary Care Unit. Coagulation values became abnormal for the first time, platelet count fell to 1,000 per cu mm and the serum lactate dehydrogenase (LDH) level rose to 3,800 units per dl. The patient became anuric and hypotensive and died on that day.

Examination at autopsy showed a diffuse bleeding diathesis. Petechiae were noted in the endocardium, myocardium, pleura, esophagus, stomach, small bowel and liver. The lungs were moderately congested, and hemorrhage was present in the mediastinum, retroperitoneum and renal calices and pelvis. There were no gross lesions of the uncut brain. Brain cutting showed numerous petechiae in both hemispheres.

Microscopically, the characteristic lesions of TTP, finely granular hyaline thrombi of arterials showing a positive periodic acid-Schiff (PAS) reaction and associated with endothelial proliferation, were found in the heart, pancreas, adrenals, kidneys, alimentary tract, skin and brain.

DR. NAUGHTON: *This case and the subject in general of thrombotic thrombocytopenic purpura will now be discussed by Dr. Charles Linker.*

Discussion

DR. LINKER:* During the past five years, there has been greatly renewed interest in thrombotic thrombocytopenic purpura. The interest was initially prompted because of advances in therapy that were arrived at empirically. TTP now joins that small list of disorders that were once relentlessly fatal but can now be successfully treated in most instances. TTP has come under careful scrutiny in the laboratory, particularly because of the suggestion that a currently unknown plasma factor might be responsible for this bizarre disorder. At this time, the laboratory findings are

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tantalizing and interesting, but not definitive. The case presented here is an excellent example of the current state of our knowledge of TTP. Our therapy was almost successful but then failed. The crux of the problem is that it is difficult to treat a disorder when one does not understand its nature. I would like to review briefly the clinical characteristics of TTP and then discuss in detail two other aspects—the current state of therapy for the disorder and of investigation of its pathogenesis.

At present, TTP really cannot be precisely defined, and a definition has to be more or less descriptive. Thrombotic thrombocytopenic purpura is a syndrome characterized by a constellation of the classic pentad of findings: microangiopathic hemolytic anemia, thrombocytopenia, a variety of neurologic signs that often fluctuate, fever and some sort of renal disease.[1] TTP usually affects young people, with a slight female predominance (Table 1). Occasionally there is a prodromal flulike illness. A patient presents to a physician because of neurologic symptoms, bleeding, symptoms of anemia or abdominal complaints. At times the abdominal symptoms overshadow the others and a patient will undergo an exploratory laparotomy or be treated for inflammatory bowel disease before the hematologic aspects of the case are appreciated. Common findings on physical examination include fever, bleeding, pallor and a variety of neurologic findings.

Because the neurologic findings in this disease are so peculiar and so characteristic, they deserve a detailed description. There are often generalized findings of headache and decrease in level of consciousness, which may be as severe as coma. There are also focal symptoms of paresis, aphasias, dysarthrias and, usually in the terminal and uncontrolled phase of the disease, seizures. The most prominent aspect of the neurologic picture is that these findings can be evanescent. One may find a patient with a right hemiparesis, proceed to demonstrate this finding to a colleague, only to find the patient to be normal or to have a left hemiparesis. Similarly, one may find a patient with a classic receptive aphasia, leave the room and return to find the patient either in a normal state or comatose. Any theory of the pathogenesis of TTP must account for this unusual picture in which severe mental status and neurologic findings can come and go literally in a matter of minutes.

The diagnosis of TTP is made primarily by laboratory findings (Table 2). The hallmark of the disorder is microangiopathic hemolytic anemia characterized by an anemia that is usually severe, a reticulocytosis and, most importantly, red cell fragmentation on a peripheral blood smear. One will see burr cells and schistocytes, triangular forms and other varieties of abnormally shaped red blood cells that are thought to be produced by mechanical fragmentation. The diagnosis of TTP is untenable if red cell fragmentation is not an impressive part of the picture. Other concomitants of a hemolytic state may be present, including a high serum LDH, elevated bilirubin, hemoglobinuria and occasionally hemoglobinemia. Of importance is that the Coombs' test should be negative. Other laboratory features include thrombocytopenia that is usually severe and accounts for the bleeding disorder. The coagulation studies, by which I mean the prothrombin time, partial thromboplastin time, fibrinogen and thrombin time, should be normal. The presence of moderate amounts of fibrin-split products is a nonspecific finding and does not detract from the diagnosis of TTP.

Kinetic studies in TTP have shown that this is

TABLE 1.—*Clinical Features of Thrombotic Thrombocytopenic Purpura (TTP)*

Age: Usually 10-40 years
Sex: Female predominance (60%)
Occasional prodromal illness
Presenting symptoms
Neurologic symptoms
Bleeding
Pallor, weakness
Abdominal pain, nausea, vomiting
Findings on physical examination
Fever
Hemorrhage
Pallor
Neurologic findings

TABLE 2.—*Laboratory Features of Thrombotic Thrombocytopenic Purpura (TTP)*

Microangiopathic hemolytic anemia (MHA)
Anemia, often severe
Reticulocytosis
Red cell fragmentation
High lactate dehydrogenase
Negative Coombs' test
Elevated serum bilirubin level
Hemoglobinuria
Thrombocytopenia
Usually severe
Normal coagulation parameters
Except for elevated fibrin-split products
Abnormal urinary sediment

a disorder of accelerated platelet turnover, with normal fibrinogen turnover.[2] Platelet life is short and the calculated turnover is three to four times normal. Studies using radiolabeled platelets have shown that their uptake is not spread diffusely through the vascular system as one might expect, but rather it appears that injured platelets are taken up in the reticuloendothelial system. Red blood cell survival is short, as shown by studies of chromium-labeled red blood cells and by the clinical observation that red blood cell transfusion fails to raise the hematocrit level.

Our current concept of microangiopathic hemolytic anemia is illustrated by the rather striking picture of red cells that have been forced in vitro through a tube in which fibrin strands were created. These red cells are sheared across fibrin strands and then resealed in a variety of bizarre forms.

The histopathology of TTP is characterized by the *hyaline thrombus*. These thrombi are found throughout the vascular system, with predominant involvement of the brain, heart, kidney, pancreas and adrenal gland. These thrombi do not consist of red blood cells but of platelets and fibrin. This has been documented by electron microscopy and immunochemical staining. When the lesions are studied in detail by electron microscopy, one finds a spectrum of abnormalities: simple endothelial cell swelling, vessels with open lumens but subendothelial deposits of hyaline material, vessels with lumens occluded by loose platelet aggregates and, finally, occlusive thrombi. As one would expect from the description of the transient nature of the neurologic findings, infarction is seldom found.

In Amorosi and Ultmann's classic review in 1966,[1] most of the patients died within three months, and in their study of over 200 patients there were only 15 long-term survivors, defined as those surviving more than a year. Thus we have a composite clinical picture of TTP as a bizarre disorder affecting primarily young women, characterized by increased red cell and platelet turnover without participation of the coagulation system, in which available evidence appears to indict some abnormality of the platelet and the endothelial cell.

Before making a definitive diagnosis of a poorly characterized disease such as TTP, one must ask, "What else could it be?" Fortunately, most cases of TTP are fairly distinctive and the diagnosis is straightforward. Nevertheless, there are other disorders that can mimic some of its manifestations

TABLE 3.—*Differential Diagnoses of Thrombotic Thrombocytopenic Purpura (TTP)*

Disseminated intravascular coagulation (DIC)
Evans' syndrome
Vasculitis
Systemic lupus erythematosus
Severe glomerulonephritis
Other
Other causes of microangiopathic hemolytic anemia (MHA)
Vascular malformations
Prosthetic valves
Metastatic adenocarcinoma
Malignant hypertension
TTP-like syndromes
Hemolytic-uremic syndrome
Postpartum acute renal failure
Eclampsia

(Table 3). The most important disorder to exclude is disseminated intravascular coagulation (DIC), which certainly can lead to the presentation of an ill and febrile patient with bleeding and some red cell fragmentation. The important point to recognize is that DIC is primarily a disease of the coagulation system and that the coagulation tests should be grossly abnormal. With TTP, despite the severity of the illness and despite severe thrombocytopenia, there is no coagulopathy. Evans' syndrome describes the coexistence of immune thrombocytopenia and immune hemolytic anemia and could be confused with TTP. Importantly in TTP the Coombs' test should be negative, and in an immune-mediated process red cell fragmentation should not be present.

The vasculitic disorders can be the most difficult to differentiate from TTP. They share in common disruption of the endothelium—which may lead to platelet aggregation—and red cell fragmentation. Whatever the underlying cause of the endothelial abnormality, the resulting phenomena may appear similar. The distinction between TTP and vasculitis is best made on the basis of the composite clinical picture. On occasion a biopsy of involved vessels may be useful in making the diagnosis, inasmuch as the inflammatory lesion of vasculitis will appear quite different from the hyaline thrombus of TTP. In some cases the distinction between vasculitis and TTP becomes a matter of semantics; systemic lupus erythematosus occasionally causes a syndrome indistinguishable from TTP.

Because the microangiopathic finding is the laboratory hallmark of TTP, other causes of microangiopathy need to be considered. Vascular mal-

TABLE 4.—*Proposed Therapies for Thrombotic Thrombocytopenic Purpura (TTP)*

Steroid agents	Plasma infusion
Splenectomy	Vincristine sulfate
Antiplatelet agents	Prostacyclin infusion
Plasma exchange	

formations, prosthetic valves, metastatic adenocarcinoma and malignant hypertension are usually easy to distinguish from TTP, however. Lastly, what I have called the TTP-like syndromes may be difficult to separate definitively from TTP because one is dealing with a spectrum of disorders that most likely have the same underlying pathophysiology, rather than being totally different diseases. The adult form of hemolytic-uremic syndrome and its variant, postpartum acute renal failure, are part of a TTP-like spectrum. Eclampsia is usually distinctive but on occasion merges with TTP.

Treatment of TTP

Having made a definitive diagnosis, one must face the very difficult issue of treatment. The variety of proposed therapies is testimony to the fact that none is perfect (Table 4).

Glucocorticoid preparations alone are ineffective in this disorder. Because adrenal hemorrhage is commonly seen in thrombotic thrombocytopenic purpura, one can argue that a very ill patient should be given steroids to prevent addisonian crisis, but this is a secondary use of such treatment. Almost all patients with TTP receive steroids in addition to other therapies, so it is impossible to assess whether they may have some use in an adjunctive role. However, glucocorticoid agents should not be relied on as primary therapy.

Splenectomy is the time-honored form of treatment of TTP, and in Amorosi and Ultmann's review[1] the only patients with long-term survival were those treated with splenectomy. Dr. Cuttner[3] at Mt. Sinai Hospital has recently summarized her ten-year experience with splenectomy for TTP. Of 18 patients, 13 showed response, and when she excluded those patients who had not also received dextran intravenously, a very impressive 87 percent response rate was seen. Other investigators have also observed that patients respond to splenectomy, including those who have failed on a trial of plasma exchange. Despite these excellent results, most investigators do not recommend splenectomy as the first line of therapy for thrombotic thrombocytopenic purpura. Other groups have not seen a high response rate to splenectomy. Also, one must consider the problems of operating on an acutely ill patient with thrombocytopenia who may not benefit from platelet transfusions. Furthermore, less invasive procedures may be more or equally effective. I am convinced from published evidence that splenectomy does have some role in the treatment of TTP, but I reserve its use for patients who have failed to respond with primary therapy. The rationale for the use of splenectomy is obscure and its use is entirely empiric.

Antiplatelet agents have been used for over ten years in the treatment of TTP.[4] The rationale is clear. Patients with prosthetic valves have accelerated platelet turnover without accelerated fibinogen turnover, the same as in TTP. The combination of aspirin and dipyridamole can reduce systemic emboli and can correct the altered platelet turnover. Hence these drugs might be expected to correct the platelet disorders of TTP. Antiplatelet agents have been used occasionally as the sole form of therapy for TTP and some patients have responded. However, the bulk of information about antiplatelet agents concerns their use as the second, third, fourth or even fifth line of therapy in combination with other modalities. Several studies show[5] a beneficial effect of such therapy. Some patients treated with dipyridamole have not responded initially but eventually have to higher doses of this agent. Additionally, patients have appeared to respond to combinations of treatments, including antiplatelet agents, to relapse when the antiplatelet agents were withdrawn and to re-respond when they were reinstituted. Although antiplatelet agents have contributed to the treatment of some patients, their importance is difficult to assess. Certainly they should not be used as the only therapy. Whether their therapeutic benefit in some patients will outweigh the increased bleeding risk resulting from the addition of a platelet-inhibiting agent to a patient who is bleeding and has thrombocytopenia is currently unknown and can be answered only by careful clinical trials.

Considerable progress was made in the treatment of TTP in 1976 when Bukowski and coworkers[6] reported their results with exchange transfusion. Previous results with other forms of therapy, including steroids and splenectomy, were extremely disappointing, with a mortality in the range of 90 percent to 95 percent. With this new therapy, not only did some patients recover, but, almost like Lazarus, four of six patients recovered from coma or dense neurologic abnormalities

TABLE 5.—*Hypotheses Regarding Pathogenesis of Thrombotic Thrombocytopenic Purpura (TTP)*

Cytotoxic anti-endothelial cell antibodies
Absence of inhibitor of platelet aggregation
Absence of prostacyclin-stimulating factor
Absence of prostacyclin-stabilizing factor
Decreased fibrinolytic activity in endothelial cells

within 12 to 24 hours of exchange transfusion. The following year Bukowski and associates[7] reported the use of plasmapheresis without red cell transfusion but with similarly dramatic results. Other investigators[8] have also reported not only that a sizable fraction of patients (approximately 60 percent to 70 percent) respond to such therapy, but that dramatic recovery from coma and from other neurologic abnormalities may occur during or shortly after plasma exchange. It has been argued that we are misinterpreting the responses to plasma exchange and that improvement with therapy for TTP is the result of better support modalities and the recognition of milder cases. That argument is not tenable. Improved support is important and these patients do need blood products; however, the repeated observation of dramatic recovery during or immediately after plasma exchange is impressive, certainly to those involved in the care of these patients. My review of the literature has yielded 70 cases treated with plasma exchange, with a 70 percent response rate. Thus it is a therapy that works well in most cases. In some cases, as in the case discussed here, it fails. Because of its effectiveness, rapidity of action and relative lack of toxicity, plasma exchange is now the first line of therapy for TTP.

In 1977 Byrnes and Khurana[9] created a small sensation by reporting the effectiveness of simple plasma infusion for TTP. They treated a case of TTP with plasma exchange using fresh frozen plasma as the replacement fluid. When they used albumin alone as replacement, the patients relapsed. When they simply infused fresh plasma without plasma removal, the patients responded. In one patient either fresh frozen or outdated plasma would correct the disorder. In 1980 Byrnes[10] updated these results and reported 14 of 19 patients responding to plasma infusion as their sole therapy. Other investigators have confirmed these results in occasional patients, particularly those with chronic TTP. Upshaw[11] reported a case of a congenital TTP-like syndrome that responded to small-volume plasma infusion. However, many patients have failed on plasma infusion and then responded either to plasma exchange or to other forms of therapy, such as splenectomy and steroid agents.[12] At present, plasma infusion should not be used as the sole form of therapy for patients with typical fulminant TTP. Some will respond, but those who require additional therapy may deteriorate irreversibly while this therapy is failing. Plasmapheresis is a more inclusive treatment and should be used initially.

Recently two new modes of therapy for TTP have been described. The *Vinca rosea* alkaloids, vincristine and vinblastine, have been used with apparent success in eight reported cases. Some of these patients had failed to respond to more conventional treatment, and in some vincristine sulfate was the sole agent. The mechanism of action of vincristine in this circumstance is obscure and the role of this agent in therapy remains to be determined. Prostacyclin infusion has been attempted in several cases in which conventional treatment failed. The rationale for its use is clear: it should prevent the platelet aggregation that presumably causes vascular occlusions. This therapy has failed in several cases but has been successful in one instance. Information regarding the use of prostacyclin in this disorder is clearly preliminary.

Pathophysiology

I should like to move now to a discussion of the pathophysiology of TTP. Most students of TTP feel that an interaction between platelets and endothelial cells is responsible for the disorder. Whether the platelet aggregation abnormality is primary with secondary endothelial damage, or whether endothelial damage comes first and platelets adhere secondarily, or whether there is some subtle interaction between these two cell types is not at all clear. A number of hypotheses have been advanced regarding the precise mechanism (Table 5). From the large number of hypotheses proposed, it is clear that no explanation is widely accepted. At present, the following should be viewed as preliminary and as pertaining perhaps only to small subsets of TTP.

Some cases of TTP appear to be genetic in origin. The evidence for this is twofold. TTP has been reported several times in siblings. In some cases the disease has been unprovoked, but in one remarkable circumstance, fatal TTP developed in two sisters during their pregnancies. In adult hemolytic-uremic syndrome, a similar pattern of

sibling predisposition has been reported. In addition to these cases, reports of relapsing TTP have also been documented, suggesting that a patient may be prone to have the disorder develop but it may require some inciting event. The nature of the possible genetic predisposition is unknown. One report has suggested a human leukocyte antigen (HLA) linkage.

Kwaan[13] has proposed that a defect in vascular fibrinolytic activity is responsible for the disorder. He finds that endothelial cells from blood vessels of TTP patients have reduced ability to lyse fibrin when they are plated in vitro on fibrin-coated dishes. In contrast, endothelium adjacent to areas of "unusual" thromboses has normal or enhanced fibrinolytic activity in this assay. It is difficult to assign a causative significance to this observed phenomenon. Current assays of fibrinolytic activity may not be physiologically relevant. Also, decreased fibrinolytic activity could be a secondary phenomenon, the result of endothelial cell damage of any cause.

A circulating toxin to endothelial cells has been postulated as the primary problem in TTP. Wall and co-workers[14] have reported eight cases in which they showed an IgG antibody that would support complement-mediated lysis of endothelial cells in the presence of rabbit complement. Other investigators have reported similar findings. Problems with all these reports are that anti-HLA antibodies would also be detected in this system and that these patients are multiply transfused and often previously pregnant. At this time, the weight of evidence is against TTP's being an immunologic-mediated disorder. TTP cases during pregnancy have been associated with thrombi only in the maternal circulation; if an IgG factor were responsible one would expect the fetus to be affected as well.

Normal plasma may contain a previously unsuspected inhibitor of platelet aggregation (platelet-aggregating factor inhibitor, PAFI), with the defect in TTP being the absence of this inhibitor.[15] Observations by Lian and Savaraj in support of this are as follows: When they add TTP plasma to normal platelets that have been washed free of plasma proteins, the platelets agglutinate. Normal plasma does not cause this agglutination. This effect of TTP plasma is not inhibited by standard antiplatelet agents or by prostacyclin. The effect is neutralized by dilution of TTP plasma with normal plasma, and this correction is dose-dependent and time-dependent. Two different PAFI's—one an immunoglobulin and one with high molecular weight that can neutralize the platelet-aggregating effect of TTP plasma—were reported to be purified. Although Lian and Savaraj's concept is interesting, few investigators have reproduced their finding of the platelet-aggregating factor (PAF) in TTP plasma, and the finding is restricted to a small number of cases. Most cases appear to lack PAF. One strength of Lian and Savaraj's proposal is that it would explain the efficacy of plasma infusion therapy in the restoration of PAFI. This hypothesis is currently preliminary, however, and requires further development.

With all the recent interest in prostaglandin metabolites mediating the interaction between platelets and endothelial cells, prostacyclin metabolism became a logical target of inquiry in TTP. Remuzzi and associates[16] in 1980 made the following observations. When normal plasma is added to endothelial cells in culture, they are stimulated to make prostacyclin. TTP plasma lacks this stimulatory ability. After one patient was successfully treated with plasma exchange, this stimulatory defect was corrected. Even more interesting, another patient in remission had persistence of this defect and two of the four children of this patient had the same in vitro deficiency. Such a deficiency might explain the apparently genetic predisposition to TTP. One other investigation has confirmed these results.[17] Prostacyclin is far more stable in plasma than it is in buffer for reasons that are unclear. Chen and co-workers[17] have reported that this enhanced prostacyclin stability is not mediated by TTP plasma but that the defect is corrected by the addition of normal plasma. Wu and colleagues[18] have studied radiolabeled prostacyclin that has been incubated with normal plasma and fractionated by gel filtration. In normal plasma, prostacyclin binds to a very high molecular weight component that elutes in the void volume. This high molecular weight factor was absent in TTP plasma. These studies regarding prostacyclin must be viewed cautiously. There may be no normal circulating endogenous prostacyclin. If this is true, observations concerning the fate of exogenous prostacyclin may not be physiologically relevant.

Conclusion

The TTP syndrome represents a heterogeneous spectrum of abnormalities, some of which are chronic and possibly hereditary, but most of which are fulminant. Although the pathogenesis appears

to operate through a final common pathway of platelet-endothelial cell interaction that causes vessel occlusion, several different basic mechanisms likely lead to the same result. The basis of this disorder remains obscure. The current therapy of choice for this disorder is frequent large-volume plasma exchange using fresh frozen plasma as the replacement fluid. We currently perform exchanges daily, each time replacing a volume equal to 1½ to 2 times a patient's calculated plasma volume. Plasmapheresis is continued until a patient achieves clinical and hematologic remission. Red cell fragmentation may continue to be apparent on a peripheral blood smear for prolonged periods and is not by itself an indication for continuing treatment. In our experience maintenance therapy is usually not necessary.

Whether adjunctive therapy with antiplatelet agents or other modalities help more than they hurt cannot yet be answered but will likely be addressed in ongoing clinical trials. The efficacy of other therapeutic agents such as vincristine is also uncertain. However, in approaching a patient with TTP, one must be open-minded with regard to changing treatment regimens that are not rapidly effective. Because TTP is a heterogeneous disorder, different patients respond to different therapies. If a patient is not responding well to first-line therapy, this must be quickly recognized and a different approach taken. The combination of splenectomy, dextran and glucocorticoid agents is the second-line therapy of choice. Definitive therapy for TTP awaits the elucidation of the basic pathophysiology of the disease.

REFERENCES

1. Amorosi EL, Ultmann J: Thrombotic thrombocytopenic purpura—Report of 16 cases and review of the literature. Medicine (Baltimore) 1966 Mar; 45:139-159

2. Harker L, Slichter S: Platelet and fibrinogen consumption in man. N Engl J Med 1972; 287:999-1005

3. Cuttner J: Thrombotic thrombocytopenic purpura and dose of plasma exchange. Blood 1980; 54:302-306

4. Amorosi EL, Karpatkin S: Anti-platelet treatment of thrombotic thrombocytopenic purpura (Editorial). Ann Intern Med 1977; 86 102 108

5. Myers T, Waken CJ, Ball ED, et al: Thrombotic thrombocytopenic purpura—Combined treatment with plasmapheresis and anti-platelet agents. Ann Intern Med 1980; 92:149-155

6. Bukowski RM, Hewlett JS, Harris JW, et al: Exchange transfusions in the treatment of thrombotic thrombocytopenic purpura. Semin Hematol 1976 Jul 16; 13:219-232

7. Bukowski RM, King JW, Hewlett JS: Plasmapheresis in the treatment of thrombotic thrombocytopenic purpura. Blood 1977 Sep; 50:413-417

8. Pisciotta A, Garthwaite T, Darin J, et al: Treatment of thrombotic thrombocytopenic purpura by exchange transfusion. Am J Hematol 1977; 3:73-82

9. Byrnes J, Khurana M: Treatment of thrombotic thrombocytopenic purpura with plasma. N Engl J Med 1977; 297:1386-1389

10. Byrnes JJ: Thrombotic thrombocytopenic purpura. Adv Intern Med 1980; 26:131-157

11. Upshaw JD Jr: Congenital deficiency of a factor in normal plasma that reverses microangiopathic hemolysis and thrombocytopenia. N Engl J Med 1978 Jun; 298:1350-1352

12. Ansell J, Beaser RS, Pechet L: Thrombotic thrombocytopenic purpura fails to respond to fresh frozen plasma infusion. Ann Intern Med 1978; 89:647-648

13. Kwaan H: The pathogenesis of thrombotic thrombocytopenic purpura. Semin Thromb Hemostas 1979; 5:184-198

14. Wall RT, Harker LA, Striker G, et al: Human endothelial cell injury mechanisms in vitro. Thromb Haemost 1977; 38:228-229

15 Lian E, Savaraj N: Effects of platelet inhibitors on the platelet aggregation induced by plasma from patients with thrombotic thrombocytopenic purpura. Blood 1981; 58:354-359

16. Remuzzi G, Mecca G, Livio M, et al: Prostacyclin generation by cultured endothelial cells in hemolytic uremic syndrome (Letter). Lancet 1980; 1:656-657

17. Chen Y, Hall ER, McLeod B, et al: Accelerated prostacyclin degradation in thrombotic thrombocytopenic purpura. Lancet 1981; 2:267-269

18. Wu KW, Hall ER, Papp A: Prostacyclin stabilizing factor deficiency in thrombotic thrombocytopenic purpura. Lancet 1982 Feb; 1:460-461

Important Advances in Clinical Medicine

Epitomes of Progress — Plastic Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in plastic surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in plastic surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Tangential Excision and Choice of Donor Sites

THE MOST NOTABLE ADVANCE in burn therapy to reduce morbidity and mortality since the advent of topically administered antibiotics is the development of the technique of tangential excision and immediate grafting. Although introduced in Europe a decade ago, this concept of burn wound treatment is only now achieving wide popularity among burn surgeons in the United States. Whereas superficial second-degree burns usually heal well with topical administration of antibiotic medications, deeper second- and third-degree burns require long periods of painful dressing changes and open wounds, increasing morbidity and mortality from invasive sepsis. The previously accepted concept of burn wound treatment was to permit those areas that were capable of healing on their own to do so, allowing the deeper wounds to develop granulation tissue that could then be grafted. However, granulation tissue, filled as it is with bacteria and myofibroblasts, promotes scar contraction and infection. Wound contraction leads to joint contractures and further disability.

For adults and children with burns of up to 60 percent of total body surface, excising the wound in successive stages (15 percent to 20 percent of the burn wound at each session) is now advocated. This is done with a skin graft knife, peeling layers of burn eschar down to living dermis, or the *zone of stasis*. The exposed wound can then be covered immediately with autograft or, if donor sites are not available, they may be covered with a suitable biologic dressing (preferably homograft or fresh meshed porcine heterograft) until donor sites become available. This minimizes deformity, removes a source of infection and permits a shorter hospital stay and improved cosmetic result.

The importance of careful selection of donor sites for this technique cannot be overemphasized. The use of the scalp as donor site in these patients has made available additional, usually uninjured tissue for the grafting procedure. Thin sheets of autograft of 0.25 to 0.30 mm (0.010 to 0.012 inches) can be taken from the scalp, which has been infused with a saline solution to facilitate removal of the skin. The donor site will reepithelialize rapidly when dressed with Op-Site or other polyurethane film dressing (five to seven days) and may be reused on a weekly basis until the entire burn wound has been excised and grafted. Scalp tissue has advantages in that it is a relatively painless donor site, it is quite durable for meshing, it heals rapidly due to the large amount of hair follicles and sebaceous glands and, most im-

portant, with the regrowth of hair *it is the only truly hidden donor site.* This is an important consideration for burn victims, who often will have few parts of their body that have not been scarred either by the burn or by the surgeon's dermatome.

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REFERENCES

Berkowitz RL: Scalp—In search of the perfect donor site. Ann Plast Surg 1981 Aug; 7(2):126-127

Hunt JL, Sato R, Baxter CR: Early tangential excision and immediate mesh autografting of deep dermal hand burns. Ann Surg 1979 Feb; 189:147-151

Janzekovic Z: A new concept in the early excision and immediate grafting of burns. J Trauma 1970 Dec; 10:1103-1108

Surgical Treatment of the Hand

WITH THE ESTABLISHMENT of the *Journal of Hand Surgery* and two national hand societies, the field of surgical treatment of the hand is now identified as a subspecialty. Training programs in surgical procedures on the hand in existing residency programs and free-standing fellowships are providing specialized training, and the programs themselves are being evaluated and standardized. There has been a tremendous expansion of surgical techniques on the hand with the evolution of microsurgical replantation and transplantation. Digital and hand replantations, a curiosity a few years ago, are now becoming routine and the results are being evaluated on the return of function to the replanted part, rather than mere survival. Reconstruction of thumbs and fingers by toe transplant is becoming more widely accepted. Multiple digits have been reconstructed by transplanting two adjacent toes or single toes from each foot. The thumb has been reconstructed with the transplantation of the large toe, the second toe, portions of the large toe, neurovascular island flaps combined with bone grafts and even thumb transplants from a functionless opposite hand.

Results after replantation of amputated digits and hands have been improved by careful attention to maintenance of bone stability with the primary use of intramedullary bone pegs, polyglycolic acid pegs, transverse intramedullary bone wires and improved instrumentation for inserting pins and small plates.

Other composite tissues have been transplanted to the hand with microneurovascular anastomosis, including metatarsal joints, osteocutaneous grafts from the hip and vascularized fibular grafts to forearm bone defects. However, these composite transplants have yet to withstand the test of time. Well-documented series of the correction of congenital defects, such as a radial clubhand, by classical techniques, remain the preferred method of treatment.

Nerve entrapment syndromes continue to be a diagnostic challenge in the field of surgery. Carpal tunnel syndrome is well recognized but ulnar compression syndromes, radial nerve compression problems and combined nerve compression problems are being recognized more and more.

Expanding interest in muscle transplantation from the lower to the upper extremities and muscle transfers within extremities have spurred interest in muscle anatomy and function. Fiber length and volume have become established as the key guidelines to consider with any transplant or transfer.

The replacement of old joints with new joints continues to be an area of special interest in surgical procedures of the hand. Though silastic implants are popular, tendon spacers and fusions must be considered.

Hand infections, once a major part of surgical treatment of the hand, are uncommon today; however, infections by normal flora and fungi are being reported, particularly in people on long-term steroid therapy. Congenital anomalies of the hand also present a challenging reconstructive problem. A better understanding of the management of these defects requires careful classification. Classic methods of treatment have always served as a standard against which new operations must be measured. Alternate flaps and alternate methods of reconstruction must always be considered.

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REFERENCES

Brand PW, Beach MA, Thompson DE: Relative tension and potential excursion of muscles in the forearm and hand. J Hand Surg 1981 May; 6:209-219

Flatt AE: New joints for old. J Hand Surg 1980 Nov; 5:525-527

Wang SH, Young KF, Wei JN: Replantation of severed limbs—Clinical analysis of 91 cases. J Hand Surg 1981 Jul; 6:311-318

Current Trends in Treating Giant Pigmented Nevi

ALTHOUGH SOME controversy persists regarding frequency, there are numerous reports of high risk of malignancy in giant nevi. Reports vary from 1 percent to 15 percent in clinical series, and up to 42 percent in pathology series. Physicians at some institutions with large series of giant pigmented nevi have stated that they have never seen a case of a malignancy in one. Perhaps the best documented long-term series is from the Danish Birth Registry with a 17-year follow-up that reports a 3.3 percent incidence (4/117). However, the risk

is much lower for small nevi and these statistics do not apply for nevi less than 0.1 sq cm. Criteria have been established that histologically distinguish congenital nevi from acquired nevi. One of the most important characteristics of congenital nevi is the presence of a neural cell with neural-Schwann cell appearance in the deep dermis and fat.

The anatomic distribution of malignancy is characteristically in the posterior paravertebral zone from occiput to coccyx. Of reported cases, 95 percent occur on the posterior cranium, back and buttocks.

The age at which malignant change occurs follows a bimodal pattern: a high incidence in early childhood (birth to ten years), a low incidence in adolescence and early adulthood (10 to 30 years) and increasing incidence in late adulthood (over 40 years). The bimodal age incidence correlates to some extent with pathologic features of the malignancy.

Malignant lesions occurring in early childhood are highly atypical. Pathologic diagnosis of neuroblastoma, neurofibrosarcoma, liposarcoma, rhabdomyosarcoma, myxomas and undifferentiated sarcomas are more common than classic melanoma. On the face and scalp these cell types, including fat, muscle, nerve organelles and nerve sheath and the normal melanocyte, have an embryologic derivation from neural crest. It has been suggested that these tumors are all embryonal neural crest malignancy with variable histologic patterns.

Malignant lesions can be multiple and occur in deep dermis and fat, not at an epidermal-dermal junction. Moreover, the derivation of neural crest cells from the dorsal neural tube and migration from dorsal paravertebral areas to the ventral region could explain the dermatome pattern of benign nevi and the paravertebral distribution of neural crest malignancy in nevi in children.

Malignancy in adults may occur in the paravertebral region but it is more likely to occur at other sites. Furthermore, adult malignant lesions are usually typical melanomas without embryonal neural crest features.

Treatment of large nevi is difficult because of high morbidity and the poor cosmesis from multiple surgical excisions and skin grafts. Recently, interest has been restimulated in dermabrasion as a way of managing the very large lesions that cannot be easily excised and grafted. Cosmetic results of dermabrasion are much better than with grafting. The problem of residual deep neval cells and malignant potential has not been resolved. Dermabrasion does not remove hair.

Recently a compromise approach has been described. The central paravertebral area and other atypical areas are surgically excised and directly closed (without grafts). This removes the areas of high risk. The lower risk areas laterally and anteriorly are dermabraded. Small lesions of cosmetic importance on the face can be treated with skin flaps or grafts. Radiation and lasers do not have a role in treatment.

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REFERENCES

Kaplan EN: Incidence of Malignancy in Small, Large and Giant Congenital Nevi—A Symposium on Pigmented Lesions. St. Louis, CV Mosby (In press)

Lorentzen M, Pers M, Bretteville-Jensen G: The incidence of malignant transformation in giant pigmented nevi. Scand J Plast Reconstr Surg 1977; 11(2):163-167

Mark GJ, Mihm MC, Liteplo MG, et al: Congenital melanocytic nevi of the small and garment type—Clinical, histologic, and ultrastructural studies. Hum Pathol 1973 Sep; 4:395-418

Reed WB, Becker SW Sr, Becker SW Jr, et al: Giant pigmented nevi, melanoma, and leptomeningeal melanocytosis—A clinical and histopathological study. Arch Dermatol 1965 Feb; 91:100-119

Laser Technology

THE ARGON LASER has been used since 1970 in the plastic surgical and dermatological treatment of a variety of cutaneous lesions. The unique photocoagulating properties of the argon laser (model 770, Cooper Medical/Spectra Physics) make this modality invaluable for clinical treatment of a variety of cutaneous lesions. The laser produces intense, bright light that is between 480 and 520 nm, which is in the visible light spectrum. As such, it is not expected to produce iatrogenic malignant neoplasms as did x-ray or ultraviolet radiations years ago. For clinical use, a combination of blue (480 nm) and green (520 nm) is used for more complete absorption. This wave length coincides clinically with the maximum absorption curve of both hemoglobin and melanin, thus rendering laser light highly effective in the treatment of both cutaneous vascular and pigmented lesions.

The argon laser light has several unique properties that make it particularly valuable in the treatment of cutaneous lesions. Laser light has the ability to penetrate the intact epidermis until it is absorbed by a pigmented structure in the dermis. This pigment can be hemoglobin, melanin or suspended pigment of tattoo particles. The laser light is converted to heat on absorption, and this heat produces a very selective coagulation or vaporization in the upper dermal levels. Adjacent dermal

appendages such as sweat glands and hair follicles are relatively impervious to laser light and aid in the rapid healing and re-epithelialization of the laser wound. The histologic changes of port-wine hemangiomas after laser treatment have been shown to be permanent and stable without ongoing changes, as shown by sequential yearly biopsies of treated lesions.

Many categories of lesions have been found amenable to argon laser treatment. These can be subdivided into five broad categories: vascular, inflammatory, nevi, tattoo and miscellaneous. Argon laser treatment has been used primarily for cutaneous vascular lesions, including port-wine hemangiomas, capillary or cavernous hemangiomas, "strawberry marks" of infancy, telangiectasia of the face and neck and other superficial vascular lesions. Inflammatory lesions such as pyogenic granuloma are easily treated with the argon laser. Nevoid-type lesions such as seborrheic keratoses, pigmented nevi, lentigo and café au lait spots have been treated successfully. Decorative and traumatic tattoos benefit by the argon laser as well. Miscellaneous lesions such as nevus of Ota, granuloma facial, acne rosacea and other lesions have also been successfully treated.

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REFERENCES

Apfelberg DB, Maser MR, Lash H: Argon laser treatment of decorative tattoos. Br J Plast Surg 1979 Apr; 32(2):141-144

Apfelberg DB, Maser MR, Lash H: Histology of port wine stains following argon laser treatment. Br J Plast Surg 1979 Jul; 32(3):232-237

Apfelberg DB, Maser MR, Lash H, et al: The argon laser for cutaneous lesions. JAMA 1981 May 22/29; 245(20):2073-2075

Apfelberg DB, Maser MR, Lash H, et al: Progress report on extended clinical use of the argon laser for cutaneous lesions. Lasers Surg Med 1980; 1:71-83

Breast Reconstruction

THERE ARE 40,000 to 50,000 mastectomies done in the United States each year. An ever-increasing number of these women are asking about and undergoing breast reconstruction. Many women find that the reality of the postmastectomy situation is not so bad as they had envisioned it and therefore accept their deformity without problem. However, a large percentage of these patients seek to improve their self-image through a reconstructive procedure. Postmastectomy reconstruction is fast becoming the logical next step in the treatment of breast cancer, so much so that insurance companies pay a substantial portion of hospital and surgical costs.

Reconstruction is not done immediately. Usually three to six months after the mastectomy the reconstruction is undertaken, but of course it can be carried out at any time, depending on the physician and the specific pathology of the patient's tumor. If a patient has three to four positive axillary lymph nodes, she is not regarded as an ideal candidate, but each case must be considered individually, taking into account that the quality of life is as important to these patients as is the length of it. In general, reconstruction should be delayed until chemotherapy and radiation therapy are completed, but can be done while still undergoing chemotherapy if a patient is clinically stable.

The actual reconstructive procedure involves two considerations. The first is how to reconstruct the mastectomy side, and the second is what to do with the remaining breast. Reconstruction of the mastectomy side is carried out by creating a breast mound and a nipple-areolar complex. The breast mound is reconstructed by using an implant. In most cases this is usually a silicone-gel implant placed under the pectoralis muscle. Double lumen implants, that is, a silicone-gel center with an outer envelope filled with variable amounts of saline at the time of surgical procedure, are also popular.

If a patient has had a radical mastectomy or if the existing pectoralis is inadequate, a latissimus dorsi myocutaneous flap may be used to provide cover for the implant. Abdominal flaps based on the rectus abdominus blood supply is another way of providing adequate tissue cover for the implant. Fluorescein dye is an excellent way to determine the viability of these flaps at the time of reconstruction.

The nipple-areolar complex can be reconstructed immediately or later, when the breast mound has settled into its permanent shape and position. Tissue available for the nipple-areolar reconstruction commonly includes the remaining nipple and areola, the upper-inner thigh tissue, postauricular skin, earlobe and ear cartilage.

Saving the nipple-areola from the mastectomy breast is not recommended, not so much because of the problem of implanting cancer cells but because of the fact that they tend to lose their pigment and to become distorted when transferred from either the thigh or abdomen where they have been stored.

Mastopexy, augmentation mammoplasty and reduction mammoplasty may be needed for symmetry when trying to match the remaining breast

with the reconstructed one. Depending on the pathology of the original carcinoma and a patient's family history, simple, subcutaneous or modified radical mastectomies may be necessary for the remaining breast. The mastectomy side and the remaining breast are usually treated in one surgical procedure.

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REFERENCES

Bostwick J III, Nahai F, Wallace JG, et al: Sixty latissimus dorsi flaps. Plast Reconstr Surg 1979 Jan; 63(1):31-41

Georgiade NG: Management of the nipple-areolar complex in reconstruction, chap 13, Breast Reconstruction Following Mastectomy. St. Louis, CV Mosby, 1979, p 239

Goldwyn RM: Plastic and Reconstructive Surgery of the Breast. Boston, Little, Brown, 1976, p 481

Mansfield C: Effects of radiation therapy on wound healing after mastectomy. Clin Plast Surg 1979 Jan; 6:19-26

Chronic Skin Ulceration After Radiotherapy for Cancer

SKIN ULCERS following radiation therapy continue to be a considerable problem for patients and physicians. Chronic painful, nonhealing ulcerations that worsen despite local treatment can develop in patients who may have had orthovoltage treatment 10 to 20 years ago. Even the newer techniques of supervoltage, while they spare the skin, occasionally result in the production of similar ulcers in skin or mucous membranes. Radiotherapy is being used more aggressively both for cure and palliation. The skin-sparing effects of the newer radiotherapy techniques undoubtedly deliver less radiation to the skin when therapy is directed at a deep lesion. Nevertheless, this deep delivery of radiation practically assures that if skin or mucous membrane chronic ulceration occurs, it will be on top of a heavily radiation-damaged tissue that may be particularly difficult to treat.

Traditionally, radiation skin damage and ulceration have been ascribed to microvascular occlusion. However, review of pathology specimens and of the original literature shows that such microvascular occlusion is rather sporadic in radiation-damaged tissue. Furthermore, many physicians, particularly those who operate on the head and neck, have noticed that radiated tissues, even though ulcerated, may bleed profusely from multiple small vessels when cut. Recent electron-microscopic studies in animal and human radiotherapy and in solar-radiation-damaged tissues have suggested that permanent damage to fibroblasts and fibroblast stem cells may be an important part of radiation skin damage. Rather than microvascular occlusion being the only cause, it is likely that fibroblasts permanently affected by therapeutic radiation are unable to generate enough healing potential to contract open wounds and heal surgical wounds that have been made in radiated tissue.

Clinical studies recently conducted in San Diego County have indicated a change in complications of surgical intervention for radiotherapy skin ulcers. Older literature in plastic surgical procedures suggested that radiation ulcers could be excised and either skin grafted or covered with local flaps. Such procedures have been found to have an exceedingly high complication rate. Even well-vascularized myocutaneous flaps have a complication rate of 43 percent, with the major complication being the force of gravity pulling intact flaps off heavily radiated beds. In contrast, myocutaneous flaps used for reconstruction of nonulcerated skin, such as in breast reconstruction, and omental flaps to cover full-thickness excision of chest wall have minimal complications.

In summary, recent studies of chronic radiation skin damage suggest that chronic fibroblast and fibroblast stem cell damage may be at least as important as microvascular occlusion. The changing techniques of radiotherapy are producing a different pattern of skin injury that will require more myocutaneous and omental flaps, and fewer skin grafts and local flaps, for reconstruction of these very challenging chronic wound problems.

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REFERENCES

Rudolph R: Complications of surgery for radiotherapy skin damage. Plast Reconstr Surg 1982; (in press)

Rudolph R, Arganese T, Woodward M: The ultrastructure and etiology of chronic radiotherapy damage in human skin. Ann Plast Surg 1982 (In press)

Rudolph R, Utley J, Woodward M, et al: The ultrastructure of chronic radiation damage in rat skin. Surg Gynecol Obstet 1981 Feb; 152:171-178

Orthognathic Surgical Treatment

ORTHOGNATHIC SURGICAL TREATMENT pertains to the surgical rearrangement of the dental arches and their supporting structures. The goal of these procedures is to correct the dental arch relationship and to put into normal alignment the position of the maxilla and the mandible to other structures. The techniques now available are no longer limited to correction of the mandibular lantern-jaw deformity but are used on both jaws and can also be used for detailed bony adjustments and corrections for optimal aesthetic results.

Asymmetries and overdevelopment and underdevelopment in any part of the lower facial skeleton are approached primarily by the intraoral

route. Dissection, retraction and osteotomy instruments have been developed that markedly facilitate these surgical procedures.

As the conditions that require orthognathic surgical intervention are sometimes associated with other malformations and functional problems, it may be necessary to have the patient examined and treated by a team of specialists. Both preoperative and postoperative orthodontic treatment is often necessary and preoperative evaluation and treatment plans should be developed in cooperation with an orthodontist.

It is technically possible to move the lower facial bony structures into any desired position. The important question is, in which position will the structures be stable and supported by the neuromuscular system and the various functions? In people who require both maxillary and mandibular surgical procedures, some surgeons prefer simultaneous operations. We have seen a number of problems following simultaneous repositioning of both jaws, that is, instability of corrected positions, relapse and malrotation (sagittal, frontal and horizontal). In patients where repositioning of both jaws is required, we have consistently corrected one jaw at a time and have not noted significant instability, relapse or malrotation. Each surgical procedure is first followed by a period of fixation and then by a period of bone induction treatment, which may last for several months. Despite the prolonged treatment time, our consistent long-term results justify the double procedures. At a recent national meeting, a panel of experts denied that problems exist with the simultaneous procedures, but regardless of the technique used by such experts, we have seen substantial deformities develop in a number of patients after simultaneous surgical procedures.

Anterior advancement of the mandible requiring interpositional bone grafts, as in hemifacial microsomia, has been successfully handled using bone induction treatments to establish the new bony structures, otherwise a major problem. Unfortunately, in those cases requiring bilaterial expansion and bone grafting, for example, micrognathia, two operations are necessary as each side is best handled individually. Older techniques are prone to failure.

Chin modification through various osteotomies is often a part of orthognathic surgical treatment and can improve facial aesthetics considerably. Augmentation with onlay bone grafts has been a major problem because of bone resorption. Denatured bone, which will soon be available, shows great promise as a new material for augmentation.

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REFERENCES

Glowacki J, Kaban LB, Murray SE, et al: Application of the biological principle of induced osteogenesis for craniofacial defects. Lancet 1981 May 2; 1(8227):959-962

Harvold E (Ed): Treatment of Hemifacial Microsomia. American Cleft Palate Education Foundation Monograph #1 (In press)

Body Contouring Operations

As THE MEDIA have made American men and women more aware of their bodies, there has been an increased demand for body contour surgical procedures. The major body contouring procedure is the abdominal lipectomy or the abdominoplasty. The term "tummy tuck" is unfortunate because it denotes a very minor procedure, whereas almost all of the body contouring operations are major operative procedures.

The abdominoplasty operation, when successfully done, can easily conceal all of the resulting scars within a bathing suit line.

Some of the major contouring procedures on the thighs and hips are more difficult, and because of a patient's motion and sitting, the scars have a tendency to widen and to be uncomfortable for a patient undergoing this type of surgical procedure. However, with modern anesthesia and concepts in reduction, operations have been devised that allow a patient to wear a modest type of bathing suit with little of the scar showing.

With the thigh contouring operations, it is difficult for patients to move after surgical procedure, and they are required to either lie or stand for at least ten days before they are able to sit. This makes it difficult with respect to all of the natural processes of elimination.

Another area of interest is the contouring of arms. All of these procedures lend themselves better to those patients who have been obese and have lost weight and have hanging segments of soft tissue fat and skin. The problem in this case is that the incision is always made down the medial aspect of the arm and is difficult to conceal on a patient who wears short sleeves.

Generally, if a defect is great enough, patients do not mind the tradeoff for the major defect with a scar. In addition, large-busted patients who undergo breast reduction are greatly improved by a reduction of the tissue in the midaxillary line, which is done at the same time as in the arm. This is called a thoracobrachioplasty.

Recently, there has been interest in the technique of *suction curettage* for patients with fatty deformities around the hips, thighs and knees. This method was first described in Europe approximately ten years ago and then was discarded because of some unfavorable results. It recently has been revived and, under certain limited circumstances, it may be an acceptable procedure. The advantage is that reduction of the deformity can be done through a small incision. The disadvantages of the procedure are that it is difficult to control blood loss and to control the accumulation of seroma in the defatted area. Limited improvement may be obtained by using this technique in and around the knees. It has also been described for areas around the ankle, but this procedure is fraught with danger.

It is suggested that patients seek consultation with several physicians qualified to do this. On the larger contour procedures, patients should be made aware that donating their own blood before surgical procedure is of great benefit. It should also be noted that all the large body contour surgical operations should be done in hospital.

FREDERICK GRAZER, MD

REFERENCE

Grazer FM, Klingbeil JR: Body Image: A Surgical Perspective. St. Louis, CV Mosby, 1980

Musculocutaneous Flaps and Free Flaps

THE AVAILABILITY of muscle in all body regions and its reliability as a transposition flap have resulted in its increasing use in reconstructive surgical procedures. Initially, muscle and musculocutaneous flaps were used for coverage of difficult wounds in which vital structures were exposed (that is, bone devoid of periosteum or infected mediastinal wounds) when traditional methods (that is, skin grafts or random local or distant flaps) were unsuccessful. The precise definition of the vascular anatomy of muscle and its overlying skin, the resistance of muscle to infection, the refinements in flap design and the ability to transplant muscle or musculocutaneous flaps to distant regions have expanded the use of these flaps for restoration of coverage, contour and function in all body regions.

Head and Neck

The microvascular transplantation of the latissimus dorsi muscle allows coverage of massive scalp defects in one operation when reconstruction by local or distant flaps is either impossible or unreliable due to prior trauma, infection or radiation injury. The pectoralis major and posterior trapezius musculocutaneous flaps are now the standard flaps for coverage of major oral, facies and neck defects associated with surgical extirpation of tumor.

Trunk

The latissimus dorsi, pectoralis major and rectus abdominis musculocutaneous flaps were initially used for immediate coverage of major, often life-threatening, truncal defects. The ability of the latissimus dorsi musculocutaneous flap to fulfill the requirements for the contour defect associated with radical mastectomy has resulted in its common use in breast reconstruction. The recent use of the rectus abdominis musculocutaneous flap allows use of the lower abdominal skin for breast reconstruction.

Pressure Sores

The lack of sensation in the skin overlying bony prominences (that is, sacrum, ischium and greater trochanter) in a patient with spinal cord injuries allows development of substantial pressure wounds. The gluteus maximus, gluteal thigh and tensor fascia lata musculocutaneous flaps are safely transferred for coverage of such defects. In selected patients with cord transection below the third lumbar level, sensation to the skin of the tensor fascia lata musculocutaneous flap is preserved by the lateral femoral cutaneous nerve. In these patients, a sensory tensor fascia lata musculocutaneous flap when transferred over these regions will provide both defect coverage and restoration of protective sensation.

Lower Extremity

The gastrocnemius and soleus muscle flaps are used for coverage of major defects in the upper and middle thirds of the leg respectively. The impact of microsurgical techniques in reconstructive surgical procedures is shown in lower third or massive leg and foot defects where local or distant flaps have often been ineffective. Both the latissimus dorsi and gracilis muscle flaps are now transplanted for defects from trauma or chronic osteomyelitis in this area, with restoration of free flap circulation by microvascular techniques. Such flaps provide vascular coverage in a single operation, avoiding delay in healing and the need for

prolonged immobility and subsequent rehabilitation.

Specific modifications of many muscle and musculocutaneous flaps are now established to allow partial muscle transposition to maintain the particular function of the muscle while still providing defect coverage. Skin-fascial flaps (that is, gluteal thigh and gastrocnemius) are based on musculocutaneous perforating vessels so that underlying muscle continuity with its origin and insertion is not disturbed. Such modifications are now standard techniques in the use of muscle and musculocutaneous flaps in all regions to provide coverage with optimal recipient-site contour and minimal donor-site deformity.

STEPHEN J. MATHES, MD

REFERENCES

Ariyan S: The pectoralis major myocutaneous flap—A versatile flap for reconstruction in the head and neck. Plast Reconstr Surg 1979 Jan; 63:73-81

Bostwick J III, Vasconez LO, Jurkiewicz MJ: Breast reconstruction after a radical mastectomy. Plast Reconstr Surg 1978; 61: 682-693

Mathes S, Nahai F: Muscle flap transposition with function preservation: Technical and clinical considerations. Plast Reconstr Surg 1980 Aug; 66(2):242-249

Mathes SJ, Nahai F: Classification of the vascular anatomy of muscles: Experimental and clinical correlation. Plast Reconstr Surg 1981 Feb; 67:177-187

McCraw JB, Dibbell DG, Carraway JH: Clinical definition of independent myocutaneous vascular territories. Plast Reconstr Surg 1977 Sep; 60(3):341-352

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EDITORIALS

Professional Roles, Status and Turf in Patient Care

THE CURRENT ASPIRATIONS of nursing for greater recognition and status as a profession and the genuine progress that is being made toward achieving these goals for nursing call attention to the broader subject of professional roles, status and turf in patient care. Aspirations for recognition and status as professionals are nothing new for workers in the vineyards of health care, and as more skills and more training are needed in more facets of patient care, there will be yet more aspirations for professional status among more kinds of health care personnel. Dentists were perhaps among the first to achieve the full perogatives and trappings of professional status. More recently pharmacists, podiatrists and optometrists have acquired academic recognition and are awarded the doctoral degree. The National League of Nursing has recently joined the American Nurses' Association in calling for all professional nurses to have at least a bachelor of science in nursing degree and some nursing schools in universities are giving great emphasis to training for masters and doctoral degrees in nursing science. Hospital administrators have adopted many of the trappings of an academic profession, but so far as a group have not actively promoted academic curricula leading to a degree although a number of such degree programs already exist. And in the offing are many other kinds of allied health personnel, health care economists, computer scientists and ethicists, to name a few, who are developing needed skills and expertise in one or another aspect of the health care enterprise. Professionalism is and has been a worthy goal of workers in the health care field and this will continue to be so.

Many physicians are disturbed by some of these trends and by their pace. A characteristic of a health profession in the modern day is that it tries to extend its turf. It is true that the overall turf of health care has expanded enormously as a result of progress in medical science and technology and government initiatives to make high quality health care available to more people. Many more skills are needed in many more places. But it is also true that the number of professionals and nonprofessionals being trained and seeking to occupy this expanded turf have also proliferated, in part again as a result of other government initiatives. Will this growing turf be large enough to support the growing needs and demands of an increasing number of health professions and professionals? How will the turf be organized? Will there be some kind of a treaty or new "etiquette" developed among "ethical" health professions for communication, coordination and accountability in health care, or will unbridled competition, perhaps mandated by an ever present capricious government, be the order of the day?

In all of this the patient who is the focus of much of this specialized attention, and who depends upon there being communication, coordination and accountability between and among health professionals, seems almost to be forgotten, as is the public, which pays the bill and can expect and demand effectiveness and efficiency in terms of the quality and cost of care received by patients. Sometimes it seems as if the raison d'être of all the health professions, that is, service to patients and to society as a whole, is almost overlooked as these professions seek to establish their roles, status and turf in patient care.

Medicine is undeniably the seminal profession in health care. Its seed pervades and is part of all the others. As the seminal profession in the health care enterprise medicine should assume the leadership. There is now a clear and present need to direct more attention to what might be called the sociology of patient care—that is, who is responsible and who does what, where and when—as well as to the economics of patient care—that is, in what ways can quality best be achieved at the least cost? There is a pressing need to study how the roles, status and turf of the now ever more numerous health professions, each with its own ambitions and special interests, can best be articulated to serve the interests of patients and the public. There is much at stake for all concerned and it is suggested that physicians provide the leadership, first in the care of individual patients and then, through organized medicine, address these issues at the local, state and national levels, in each case working closely with the other health professionals and always in the patients' and public's interest.

—MSMW

Diagnosis and Treatment of Obstructive Biliary Tract Disease

THOMAS TAYLOR WHITE has provided in this issue an overview of current methods for diagnosing and treating those diseases that cause obstruction to the flow of bile through the biliary tree. I find it difficult to take issue with what has been written; the author has been all-inclusive in his treatment of the subject. Unfortunately, the reader may be overwhelmed by the sheer bulk of material presented. Furthermore, there is little reduction, integration or resynthesis of the knowledge it provides. My remarks will be directed toward correcting this deficiency by providing a bridge between White's extensive annotation on the work published in this area and contemporary approaches to the treatment of biliary obstruction.

The variety of diagnostic techniques described by White are listed in Table 1. There obviously is no lack of procedures that a jaundiced patient can be subjected to. The history is a good starting point that, when taken with care, will suggest a reasonable working diagnosis. For example, chronic alcoholism, cholestatic drug ingestion, exposure to hepatitis or hepatotoxins and the known presence of gallstones in the gallbladder all have their diagnostic implications. A physical examination usually is nonrevealing other than in establishing the hue of icterus, size of the liver, stigmata of cirrhosis or palpable abdominal mass or tenderness. Nor are laboratory studies specific in differentiating biliary obstruction from other forms of cholestasis. The serum bilirubin determination, with its fractions, helps to distinguish those diseases that present with indirect or direct hyperbilirubinemia (hemolytic anemia, Gilbert's disease). Serum aspartate aminotransferase (formerly, glutamic-oxaloacetic transaminase) when notably elevated identifies primary hepatocellular disease. Serum albumin and prothrombin time (when corrected with vitamin K_1 oxide) determinations provide an index of hepatocellular protein synthesis that may be disturbed in chronic liver disease.

Ultrasonography has evolved as the cheapest, safest and most direct way to determine whether the biliary tree is obstructed. The finding of dilated bile ducts in a jaundiced patient is strong direct evidence of obstruction or congenital enlargement.

TABLE 1.—*Diagnostic Tools in Obstructive Jaundice*

History	Peritoneoscopy
Physical diagnosis	Visceral angiography
Liver profile	Exploratory laparotomy
Ultrasonography	Perioperative cholangiography
Radionuclide scan	Choledochoscopy
Computerized tomography scan	
Percutaneous cholangiography	
Endoscopic cholangiopancreatography	
Aspiration cytology	
Percutaneous biopsy	

The procedure may also show the cause of the obstruction by exposing the presence of gallstones in the gallbladder or a mass in the head of the pancreas. Computerized tomographic (CT) scan may be more reliable for the latter diagnosis but is more expensive and not as generally available as ultrasonography. Furthermore, CT scans expose patients to irradiation. I have attempted to place ultrasonography and CT scanning in their proper roles for jaundiced patients by the algorithm displayed in Figure 1. CT scanning is a second-order test, employed to further evaluate the details of pancreatic, bile duct or hepatic tumors.

The bile ducts should be visualized radiographically once dilatation has been shown by ultrasonography. Percutaneous transhepatic thin-needle cholangiography is the safest, most convenient and in most institutions the cheapest way to accomplish this goal. Endoscopic retrograde cholangiopancreatography is the procedure of choice when a mass has been identified in the head of the pancreas. With this approach, bile can be aspirated for cytologic examination and the papilla of Vater made visible for direct biopsy if a lesion is seen. Radiographs of the pancreatic duct may show the typical changes of pancreatic cancer. If the diagnosis is not made by this procedure, a thin-needle cholangiogram and percutaneous aspiration of the mass for cytology examination under CT scan control should be obtained.

I have purposely omitted intravenous cholangiography and radionuclide biliary scans from the algorithm because they appear to be of little value in the presence of obstruction. Visceral angiography is useful in assessing vascular involvement in pancreatic cancer and should be done in all patients who may undergo a radical pancreaticoduodenectomy. Peritoneoscopy is also of help when a direct biopsy of a hepatic lesion is required. Blind percutaneous liver biopsy is rarely needed in patients with biliary obstruction but may be of value when significant hepatocellular damage is suspected.

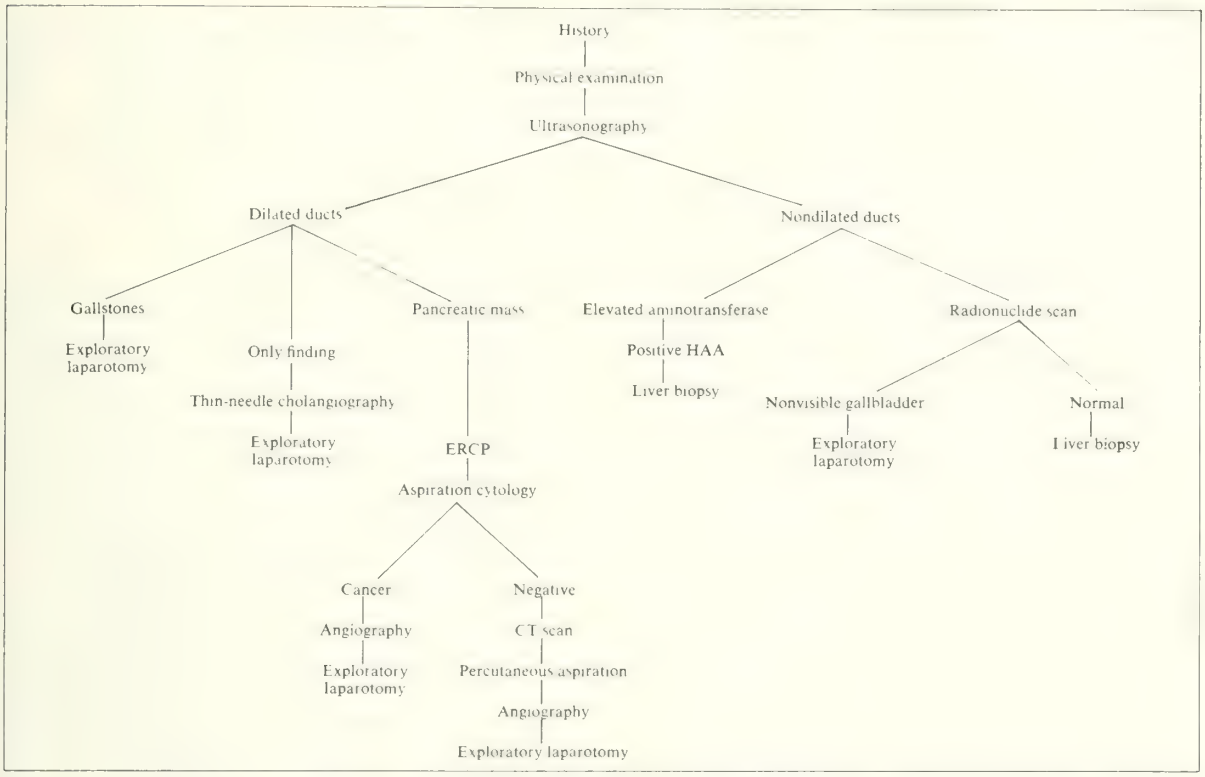

Figure 1.—Algorithm for the diagnosis of jaundice. CT = computerized tomography; ERCP = endoscopic retrograde cholangiopancreatography; HAA = hepatitis-associated antigen.

The treatment of biliary obstruction in the recent past was exclusively surgical. Today the bile ducts are easily entered from above by a radiologist and from below by an endoscopist. A variety of percutaneous and transendoscopic techniques have emerged to overcome the problem of biliary obstruction. It will not come as a surprise to you that as a surgeon I prefer the transabdominal approach for relief of obstruction. Evacuation of stones through a choledochotomy or relief of neoplastic or benign obstruction by resection or biliary-enteric bypass is my stock in trade. An exception to this preference is the percutaneous transhepatic intubation of highly obstructing neoplasms (Klatskin tumors) at or above the bile ducts in elderly patients. I also advocate the transpapillary extraction of reformed or retained stones via an endoscope in high risk surgical patients. Both of these procedures require a skilled radiologist and endoscopist. The direct surgical approach, however, is not only acceptable but likely the best approach in most cases, especially when the risk of exploratory laparotomy is not a significant factor. Further improvement in the transhepatic and endoscopic procedures will present an attractive alternative to the transabdominal route in view of their convenience, low cost and safety.

You will note that the algorithm in Figure 1 ends with exploration for all cases in which dilated ducts are observed on ultrasound studies. Then why not interpose this step between the other diagnostic steps, thus reducing the time, risk and expense involved in doing them? I believe that each step helps to improve intraoperative therapy. For example, perioperative cholangiography by either the transhepatic or endoscopic route usually identifies the level of obstruction and often its cause. Cytologic examination of percutaneous or aspiration specimens may provide a specific diagnosis, when positive, and angiography may reveal signs of vascular invasion that would preclude resection of a pancreatic mass. The operative therapy of obstructive jaundice is enhanced by having a specific diagnosis and radiographic visibility of the bile ducts before exploration.

White has considered in exquisite detail the intraoperative steps for treating the various lesions that might be encountered. I find myself in agreement with his emphasis on perioperative cholangiography in stone disease, judicious use of the choledochoscope, biliary manometry when it is

available and resection of bile duct and periampullary tumors when possible. I also concur with his advocacy of resection of choledochal cysts with Roux-en-Y jejunal reconstruction. His use of choledochoduodenostomy following secondary operations for common duct stones when the duct is dilated is also sound. I do not intend to comment on the specific therapies employed for the treatment of biliary obstruction. White's article is a comprehensive review of an important topic. The purpose of this brief editorial has been simply to highlight the use of the newer technologies of radiographic imaging to allow for accurate diagnosis and therefore early relief of biliary obstruction.

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Holism: Naissance or Renaissance?

THESE ARE fascinating times for medicine and for the medical profession. So much is happening so quickly that it is sometimes difficult to keep a perspective, or to know when to stand firm or when to try to understand and accept change. Elsewhere in this issue is a thoughtful special essay by James S. Gordon on the phenomenon now being called holistic medicine, with a sensitive discussion of its contributions and shortcomings. A growing interest in holistic medicine is one of the things that is currently happening, and so far it is receiving a mixed reception from practicing physicians. A practicing physician's attitude toward it may depend to some extent on how long ago he or she was trained and on the nature and depth of his or her personal practice experience. Many physicians will say this is nothing new, it is what they have been doing all their lives, only it was never called holistic medicine. They may add that it is too bad it is now becoming a well-publicized and well-financed focus for charlatans, quacks and anti-intellectuals to prey upon sick or unwitting persons. Others, more the products of intensive subspecialty training acquired during the years of extraordinarily productive and successful reductionist biomedical science, may tend to view it more as destructive antiscience and irrelevant if not actually harmful to good scientific patient care. But that generation is now being followed by another which in their attitudes are more like holistic "lumpers" than reductionist "splitters," and who see holistic medicine more as a conceptual framework for a more all-encompassing approach to illness and health which may add important new dimensions to doing better and feeling better for both doctors and patients.

It seems that a number of things may have been happening to bring about either a naissance or renaissance of holism in the concept and practice of medicine at this time. As Gordon points out in his essay, the burden of illness has shifted from acute infectious to chronic often stress-related diseases which often require multiple scientific and nonscientific modalities for their successful treatment. The sheer cost of modern scientific medicine has created a new interest in the possibilities for prevention of illness and injury. And the world in which people live, and become ill or stay healthy, is becoming ever more interdependent—technologically, socially, economically and even politically—with all that this implies for health care. Also there is a beginning perceptible shift away from the collective egalitarianism of the recent past toward an increased understanding of each person as a distinct and unique individual with a personal human potential to be fulfilled. These and no doubt many other forces are leading to a more holistic or even global perspective on the interactions of a whole person with his or her total environment—in illness, health and personal quality of life. With all of this the traditional physician-patient relationship is becoming more of a partnership, with the doctor's role as treater now becoming leavened with more emphasis on the even more traditional role of teacher.

Dr. Gordon has performed a service with the clarity of perception in his special essay. In many ways the more things change the more they stay the same, but somehow they always seem to get more complicated and the sameness develops new dimensions and new interrelationships. For younger physicians holism in medical practice offers the excitement of something new, an attitude or perspective much needed in a marvelous era of productive reductionist medical science. And for many older physicians the new emphasis on holism can be a comforting reaffirmation of what medicine and patient care have always been all about. These are indeed fascinating times for medicine and for the medical profession, as new perspectives and new dimensions are added to what has always been and always will be the same. —MSMW

CASE REPORTS

Refer to: Elliott CG, Hammond ME, Bond RE, et al: Renal vein thrombosis complicating lipoid nephrosis. West J Med 1982 Jun; 136:533-536

Renal Vein Thrombosis Complicating Lipoid Nephrosis

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THE ASSOCIATION between thrombosis of the renal veins and the nephrotic syndrome is well recognized.[1] Recent prospective studies have found that this complication occurs frequently among patients with membranous or membranoproliferative glomerulonephritis.[2] Less frequently documented is the occurrence of renal vein thrombosis in patients with lipoid nephrosis.[3] This report describes the case of a patient with established lipoid nephrosis and minimal glomerular pathology in whom thrombosis of the left renal vein developed.

Report of a Case

A 27-year-old man was admitted to hospital following the sudden onset of pleuritic chest pain and hemoptysis in June 1977.

Twenty-four years earlier the diagnosis of nephrotic syndrome had been established. He was treated with prednisone, which he took intermittently for exacerbations of proteinuria. Findings on a renal biopsy carried out ten years before admission were consistent with the diagnosis of lipoid nephrosis. An evaluation two years before admission showed a 24-hour urinary protein loss of 11.0 grams and a creatinine clearance of 1 ml per minute. Alternate day prednisone therapy (60 mg) was continued.

The patient was active and in good health until six months before admission when he was referred for evaluation of pleuritic chest pain and fever that had not responded to antibiotic therapy. There was no history of diuretic use. The radiograph of the chest showed a pleural based density at the right costophrenic angle. A lung perfusion scan (technetium TC 99m aggregated albumin) showed a perfusion defect in the anterolateral aspect of the right lower lobe and the accompanying ventilation scan (indium 113m aerosol) disclosed uniform distribution of airflow throughout both lung fields. Venograms of both lower extremities did not show the presence of thrombi. A diagnosis of probable pulmonary embolism was made. Heparin was administered intravenously and sodium warfarin (Coumadin) therapy was begun before discharge.

Two months before admission, treatment with sodium warfarin was discontinued in preparation for a renal biopsy. Because of heavy proteinuria (4.4 grams in 24 hours) and hypoalbuminemia (0.8 grams per dl), prednisone administration (60 mg every other day) was continued. One week before admission the patient noted a brief period of flank pain without hematuria. The day before admission pleuritic left anterior chest pain and hemoptysis developed. He had not taken diuretics and there was no history of hypertension. Physical examination disclosed a pleural friction rub over the left anterolateral portion of the chest. The blood pressure was 130/80 mm of mercury without an orthostatic decrease. Analysis of urine showed proteinuria without casts or red blood cells. Additional laboratory data included the following: hematocrit 48 percent, serum cholesterol 750 mg per dl (normal, 150 to 275), C3 component 73 (normal), C4 component 72 (high), albumin 0.6 grams per dl, blood urea nitrogen (BUN) 7 mg per dl, creatinine 1.2 mg per dl and negative results on a test for nuclear binding antibody. A peripheral smear did not show thrombocytosis. An x-ray study of the chest showed elevation of the left hemidiaphragm. A perfusion lung scan disclosed a new defect in the anterolateral left lower lobe without an accompanying ventilation defect. Selective renal venograms displayed a thrombus involving the left renal vein and extending into the inferior vena cava (Figure 1).

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Heparin was given intravenously and the patient was discharged on a regimen of sodium warfarin. Two months later he was readmitted and a percutaneous biopsy of the left kidney was carried out. The renal biopsy specimen was processed for light, immunofluorescence and electron microscopy. Twenty-two glomeruli were normal by light microscopy. The glomerular basement membranes and mesangial areas did not stain for immunoglobulins, complement, albumin or fibrinogen. Electron microscopy showed extensive fusion of foot processes without alteration of the basement membranes (Figure 2).

Discussion

Although renal vein thrombosis was originally described as early as 1840,[1] the significance of thrombi obstructing the renal veins remains unclear. Some observers suggest that renal vein thrombosis results in proteinuria and pathologic changes in the kidney, whereas others believe that thrombosis of the renal veins is a complication of the glomerular lesion. Studies have shown that acute renal vein occlusion can produce proteinuria and the nephrotic syndrome.[4] Furthermore case presentations have illustrated a decrease in proteinuria following anticoagulant therapy and improvement in renal function after dislodgement of thrombi.[5,6] Early investigators observed, however, that amyloidosis involving the glomeruli preceded renal vein thrombosis, and recent studies have implicated membranous and membranoproliferative lesions in the pathogenesis of renal vein thrombi.[3]

Unlike membranous nephropathy, lipoid nephrosis is rarely complicated by thrombosis of the renal veins. Trew and associates reviewed the cases of 70 patients with lipoid nephrosis and were unable to identify one patient in whom renal vein thrombosis developed.[7] Previous reports of lipoid nephrosis and renal vein thrombosis are available,[5,8] but in each of the patients in these reports, vigorous diuresis may have contributed to the development of renal vein thrombosis.

Both thiazide diuretics and prednisone are associated with pulmonary artery thrombosis in children with the nephrotic syndrome.[9,10] Thiazide diuretics appear to cause nephrotic syndrome through dehydration, a finding that is clearly associated with spontaneous thrombosis. Mukherjee and associates examined coagulation measurements of three patients who were receiving daily prednisolone therapy for nephrotic syndrome.[11] In all three patients, including one with lipoid ne-

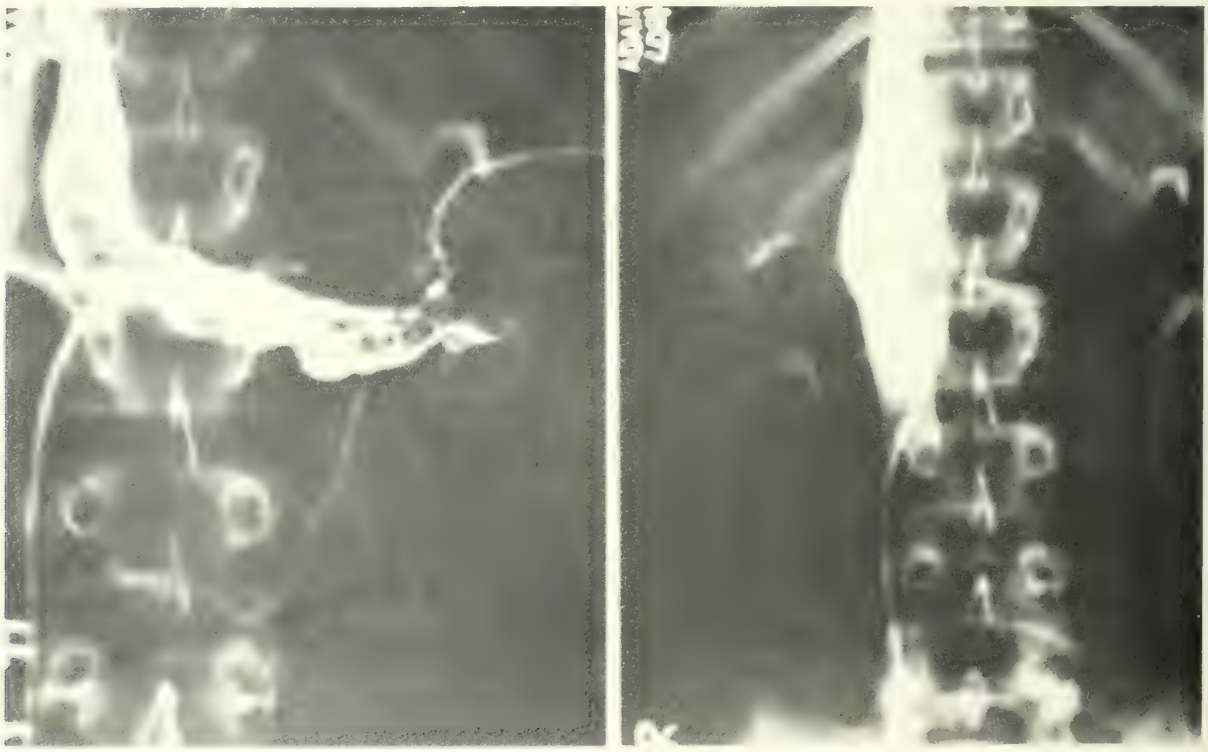

Figure 1.—Selective retrograde venography illustrates a thrombus extending from the left renal vein into the inferior vena cava.

phrosis, they found accelerated thromboplastin generation. Although our patient did not receive thiazide diuretic therapy, the high doses of prednisone on alternate days may have contributed to the development of renal vein thrombosis.

Minor histologic changes or other factors must be responsible for thrombotic complications occurring in patients with lipoid nephrosis. Light microscopic examination discloses normal glomeruli, and electron microscopy shows extensive fusion of foot processes without alteration of the basement membranes. Disordered coagulation in combination with low renal venous flow may account for the development of renal vein thrombosis. Patients with nephrotic syndrome have elevated levels of fibrinogen, factor V, combined factors VII and X, and platelets.[12] In addition, Wardle and Taylor observed impaired fibrinolysis among patients with nephrosis.[13] The excess of α_2-globulin was found to be antifibrinolytic. Although we did not find disorders of coagulation or fibrinolysis in our patient, it is possible that these factors facilitated thrombosis.

The case we discuss shows that renal vein thrombosis can complicate lipoid nephrosis. The 24-year history and the early histologic observations prove that the nephrotic syndrome preceded the thrombosis. Although the withdrawal of anticoagulation therapy may have precipitated the development of renal vein thrombosis at the time

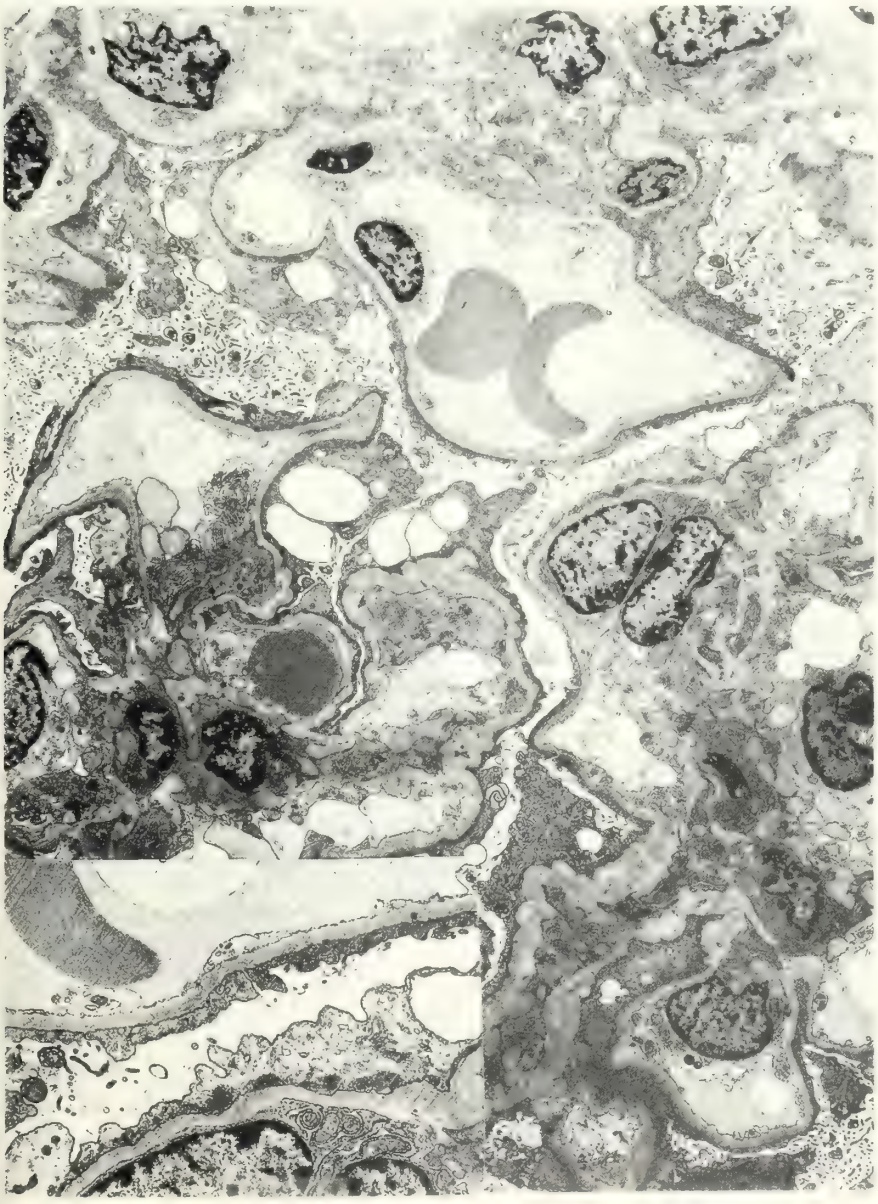

Figure 2.—Electron micrograph shows extensive fusion of foot processes along the glomerular capillary basement membrane (uranyl-acetate and lead citrate stain, reduced from original print magnification = 13,750×). The insert provides additional detail (reduced from 35,750×).

of the second pulmonary embolism, the occurrence of the first pulmonary embolism and normal venography of the lower extremities strongly suggests that renal vein thrombosis preceded anticoagulant therapy and its withdrawal. The occurrence of renal vein thrombosis in the presence of minimal glomerular pathologic findings calls into question the hypothesis that histological changes are important determinants of renal vein thrombosis. Other factors, including hypercoagulability and disordered fibrinolysis, may be important in the pathogenesis of renal vein thrombosis.

Summary

Renal vein thrombosis developed in a 27-year-old man with long-standing lipoid nephrosis. In this case recurrent pulmonary emboli suggested the diagnosis. Selective venography showed a thrombus projecting from the left renal vein into the inferior vena cava, and anticoagulant therapy was effective. Although the exact mechanism of this complication remains unclear, abnormalities of coagulation or fibrinolysis may be important since histologic abnormalities are minimal.

REFERENCES

1. Rayer P: Traité des Maladies des Reins. Paris, Balliere JB, 1840
2. Llach F, Arieff A, Massry S: Renal vein thrombosis and nephrotic syndrome: A prospective study of 36 adult patients. Ann Intern Med 1975; 83:8-14
3. Llach F, Koffler A, Finck E, et al: On the incidence of renal vein thrombosis in the nephrotic syndrome. Arch Intern Med 1977; 137:333-336
4. Omae T, Masson GMC, Corcoran AC: Experimental production of nephrotic syndrome following renal vein constriction in rats. Proc Soc Exp Biol Med 1958; 97:821-825
5. Balabanian MB, Schnetzler DE, Kaloyanides GJ: Nephrotic syndrome, renal vein thrombosis and renal failure. Am J Med 1973; 54:768-775
6. Cade R, Spooner G, Juncos L, et al: Chronic renal vein thrombosis. Am J Med 1977; 63:387-397
7. Trew PA, Biava CG, Jacobs RP, et al: Renal vein thrombosis in membranous glomerulopathy: Incidence and association. Medicine (Baltimore) 1978; 57:69-82
8. Duffy JL, Letter IJ, Cinque T, et al: Renal vein thrombosis and the nephrotic syndrome. Am J Med 1973; 54:663-672
9. Gottman N, Gross J, Mensch A: Pulmonary artery thrombosis: A complication occurring with prednisone and chlorothiazide therapy in two nephrotic patients. Pediatrics 1964; 34:861-868
10. Levin SE, Zamit R, Schmaman A: Thrombosis of the pulmonary arteries and nephrotic syndrome. Br Med J 1967; 1:153-154
11. Mukherjee AP, Toh BH, Chan GL, et al: Vascular complications in nephrotic syndrome: Relationships to steroid therapy and accelerated thromboplastin generation. Br Med J 1970; 4: 273-276
12. Kendall AG, Lohmann RC, Dossetor JB: Nephrotic syndrome: A hypercoagulable state. Arch Intern Med 1971; 127: 1021-1027
13. Wardle EN, Taylor G: Fibrin breakdown products and fibrinolysis in renal disease. J Clin Pathol 1968; 21:140-146

Refer to: Lui HK, Jacobson LB: Staphylococcal pericarditis: Successful nonsurgical treatment with indwelling catheter and antibiotic drugs. West J Med 1982 Jun; 136:536-538

Staphylococcal Pericarditis

Successful Nonsurgical Treatment With Indwelling Catheter and Antibiotic Drugs

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AN ELDERLY WOMAN with staphylococcal pericarditis was cured with antibiotic therapy and an indwelling pericardial catheter without surgical drainage. The successful outcome of this case raises the question of when surgical intervention needs to be done in this disease.

Report of a Case

A 74-year-old woman with IgG multiple myeloma of ten months' duration was admitted to hospital because of progressively severe generalized weakness and fever. She stated she did not have chest pain. She had received her fourth course of chemotherapy four weeks before admission. The only abnormalities noted on physical examination were a rectal temperature of 39.4°C and a decubitus ulcer in the sacral area. There was no pericardial rub. Laboratory studies on admission gave the following values: hematocrit, 22 percent; leukocyte count, 1,500 per cu mm with mild left shift; platelet count, 57,000 per cu mm. An electrocardiogram showed sinus rhythm at 86 per minute and ST segment elevations in leads I, II, aV_L, aV_F and V_2 through V_6. The ST segment elevations had appeared since a normal tracing that had been taken four weeks earlier. An x-ray film of the chest showed mild cardiomegaly.

The high fever in this leukopenic patient with multiple myeloma suggested infection and prompted the administration of penicillin, 1 million units intravenously every four hours. By the third hospital day, the patient was afebrile, and cultures of blood, urine and sputum specimens taken at admission were reported to be sterile. After seven days the intravenous therapy with penicillin was stopped and administration by mouth begun. On the ninth hospital day, purulent fluid draining from the sacral decubitus ulcer was cultured. On the 11th hospital day, the tempera-

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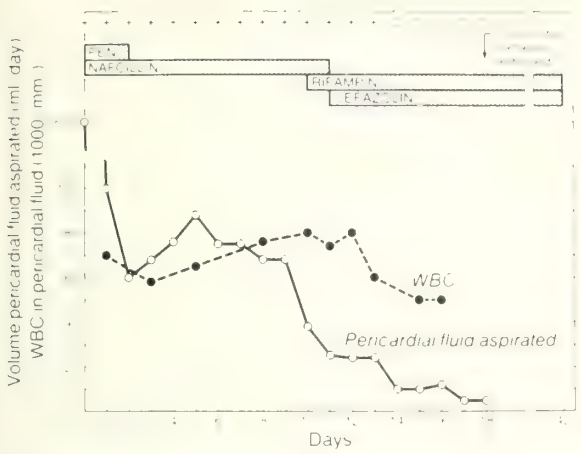

Figure 1.—Effect of pericardial drainage and antibiotic therapy on the volume and white blood cell (WBC) count of pericardial fluid: + = positive pericardial fluid cultures; 0 = negative pericardial fluid cultures.

ture, which had been normal for eight days, rose abruptly to 40°C, taken rectally. The patient looked extremely ill, but she had no chest pain.

On physical examination a regular pulse rate of 150 beats per minute was noted, with pulsus paradoxus of 10 mm of mercury, hypotension to 80 mm of mercury systolic pressure and pronounced jugular venous distention. An x-ray film of the chest showed a very large cardiac shadow. An M-mode echocardiogram indicated large anterior and posterior pericardial effusions and evidence of cardiac tamponade. Emergency pericardiocentesis yielding 600 ml of granular, purulent fluid was done using an 18-gauge Becton-Dickinson SH 2540 pericardiocentesis needle with a matched fenestrated Teflon catheter. The Teflon catheter, with a special plastic trocar to prevent clogging of the catheter lumen, was secured with its tip well inside the pericardial cavity for repeated aspirations of fluid. Gram stain of the fluid showed many neutrophils and many Gram-positive cocci, predominantly in clumps. Therapy with nafcillin sodium, 2 grams given intravenously every four hours, was initiated and the oral administration of penicillin was stopped. Intravenous administration of penicillin G was also resumed at the previous dose. Daily leukocyte counts and Gram stains and cultures of the pericardial fluid were carried out (Figure 1). Because pericardial fluid cultures grew *Staphylococcus aureus,* sensitive to nafcillin, cefazolin, rifampin and gentamicin but resistant to penicillin, the penicillin therapy was discontinued. The patient refused to have surgical drainage of the pericardium.

Despite the repeated aspiration of pericardial fluid and the intravenous administration of nafcillin, large amounts of purulent, culture-positive pericardial fluid continued to drain even ten days after the therapy was begun. Therefore, rifampin was added in a dosage of 300 mg given orally twice a day for its potential synergistic effects.[1] After 11 days of nafcillin therapy, a rash that was thought to be caused by this antibiotic appeared; the nafcillin therapy was then stopped and a regimen of cefazolin sodium (1 gram given intravenously every six hours) begun.

One day after rifampin therapy had been started, the amount of aspirated fluid began to diminish dramatically; after four days of rifampin (and three days of cefazolin) therapy, pericardial fluid cultures became sterile. After 19 days, the pericardial catheter was removed when fluid could no longer be aspirated and an echocardiogram showed no pericardial fluid. After having received a total of six weeks of antistaphylococcal therapy, the patient was discharged. When seen a year later, she felt well and had no evidence of infection and no cardiovascular abnormalities.

Discussion

This case report describes the successful treatment of purulent pericarditis with antibiotic drugs and the use of an indwelling Teflon pericardial catheter for repeated drainage of pericardial fluid. Several aspects of the clinical course deserve comment. Although electrocardiographic abnormalities compatible with pericarditis were seen at admission, the patient had no chest pain and no pericardial rub. The presence of chest pain in purulent pericarditis is unusual, having been reported in only 6 of 26 patients in one series.[2] The presence of a pericardial rub in this disease is also unusual.[2,3] In fact, the diagnosis of purulent pericarditis is easily missed because the classic symptoms and signs of pericarditis are often absent.[2]

In the past half century the spectrum of purulent pericarditis has changed with respect to the ages of the patients, the causative organisms and the factors predisposing to the development of the disease. In the preantibiotic era, patients with purulent pericarditis were generally young (mean age, 20 years), whereas now they are usually middle-aged and older (mean age, 49 years).[2,4] *Pneumococcus* was the most common infecting bacterium in the past, whereas now *Staphylococcus* and Gram-negative bacilli are the most frequently isolated organisms.[4,5] The main predisposing factors in acquiring purulent pericarditis before the availability of antibiotics were primary pulmonary

and pleural infections, most commonly pneumonia. Now, presumably because of advances in surgical techniques, antibiotic medications and chemotherapy, purulent pericarditis is seen most often in debilitated patients with impaired host defenses (such as those with carcinoma, uremia, hepatic failure, extensive burns, diabetes mellitus or leukemia and those patients receiving immunosuppressive therapy) and in otherwise healthy persons who have had extensive thoracic operations (such as an open-heart surgical procedure, penetrating thoracic injury repair and esophageal operation).[4]

Before the advent of antibiotics, surgical drainage was the only effective therapy for purulent pericarditis. Drainage resulted in about 50 percent survival in a disease that, without surgical intervention, had 100 percent mortality.[5,6] When surgical procedures could not be done, repeated pericardiocentesis was often used.[5,7] However, some authors argued that multiple aspirations of pericardial fluid could not cure the disease, and it was generally acknowledged that repeated pericardiocentesis increased the chances of serious complication. Interestingly, there were three reported cases (1921 and 1928) of patients with purulent pericarditis in whom closed pericardial drainage was done with an indwelling catheter.[8,9] In the two patients who recovered, the catheter was left in the pericardial space for periods of 28 to 41 days, without identifiable complications. Although superinfection did not occur in those two patients (or in the patient described here), it is clearly a risk of long-term catheter drainage.

Current opinion is that antimicrobial therapy alone is rarely effective in treating purulent pericarditis because pus and fluid reaccumulate, causing tamponade and creating an unfavorable milieu that decreases the effectiveness of phagocytes and antimicrobial agents.[2,5] However, a few reports describe the successful nonsurgical management of patients who were treated with antibiotic medications alone after an initial pericardiocentesis.[2,10,11] Some authors suggest surgical intervention only for those patients in whom recurrent tamponade, resistant organisms or spread of the infection occurs despite adequate and appropriate antibiotic therapy.[12] The concept that pericardiectomy may prevent or lessen the chances of a pericardial constriction developing continues to be debated. Opponents of that concept state that, in the absence of pericardiectomy, chronic constriction occurs only in patients with tuberculous pericarditis.[5,7] In our patient, surgical pericardiotomy was felt to be indicated because of persistently positive pericardial fluid cultures and reaccumulating fluid. However, as the fluid could be adequately drained by the indwelling catheter and as the patient refused an operation, surgical intervention was not done.

In this case rifampin was not used alone, for while in vitro studies have shown that many isolates of *S aureus* are sensitive to this antibiotic, clinical experience has indicated that resistance may emerge rapidly when it is the sole agent used.[13,14] Rather, rifampin was used as an adjunct to naficillin (and later cefazolin) because the pericardial fluid continued to grow *S aureus* after ten days of treatment with appropriate antibiotic drugs. Clearly, it cannot be proved that in this case rifampin, as a bactericidal drug, was the major agent sterilizing the pericardial fluid because it is possible that continuing the administration of cefazolin alone might have achieved the same beneficial result.

Conclusion

Persistent pericardial drainage via an indwelling catheter and the administration of antimicrobial agents can cure patients with purulent pericarditis. The catheter may be left in the pericardial space several days for repeated or continuous aspiration of fluid, thus avoiding risk of complications from repeated pericardiocenteses. This treatment should be considered an acceptable alternative in patients with purulent pericarditis in whom surgical intervention appears to be extremely risky.

REFERENCES

1. McCabe WR, Lorian V: Comparison of the antibacterial activity of rifampicin and other antibiotics. Am J Med Sci 1968 Oct; 256:255-265
2. Rubin RH, Moellering RC Jr: Clinical, microbiologic and therapeutic aspects of purulent pericarditis. Am J Med 1975 Jul; 59:68-78
3. Kauffman CA, Watanakunakorn C, Phair JP: Purulent pneumococcal pericarditis: A continuing problem in the antibiotic era. Am J Med 1973 Jun; 54:743-750
4. Klacsmann PG, Bulkley BH, Hutchins GM: The changed spectrum of purulent pericarditis: An 86 year autopsy experience in 200 patients. Am J Med 1977 Nov; 63(5):666-673
5. Boyle JD, Pearce ML, Guze LB: Purulent pericarditis: Review of literature and report of eleven cases. Medicine (Baltimore) 1961 May; 40:119-144
6. Adams R, Polderman H: Suppurative pericarditis. N Engl J Med 1941 Dec 4; 225:897-902
7. Cameron EWJ: Surgical management of staphylococcal pericarditis. Thorax 1975 Dec; 30:678-681
8. Whittemore W: Purulent pericarditis: A closed suction technique for drainage—Report of a case. Surg Gynecol Obstet 1921 Apr; 32:371-373
9. Harloe RF: Suppurative pericarditis: New surgical treatment of purulent pericarditis with report of two cases. Long Island Med J 1928 Nov; 22:633-640
10. Gould K, Barnett JA, Sanford JP: Purulent pericarditis in the antibiotic era. Arch Intern Med 1974 Nov; 134:923-927
11. Weir EK, Joffe HS: Purulent pericarditis in children: An analysis of 28 cases. Thorax 1977 Aug; 32:438-443
12. Horan JM: Acute staphylococcal pericarditis. Pediatrics 1957 Jan; 19:36-42
13. Massanari RM, Donta ST: The efficacy of rifampin as adjunctive therapy in selected cases of staphylococcal endocarditis. Chest 1978 Mar; 73:371-375
14. Kunin CM, Brandt D, Wood H: Bacteriologic studies of rifampin, a new semisynthetic antibiotic. J Infect Dis 1969 Feb; 119:132-137

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Cerebral Malaria, Acute Renal Failure and Disseminated Intravascular Coagulation

TO THE EDITOR: The article by Faith Fitzgerald, "Malaria: A Modern Dilemma," in the March issue is a thorough review of the problem of malaria.[1] However, one approach to the rare patient who has the most fatal constellation of signs and symptoms of malaria, cerebral malaria, acute renal failure and disseminated intravascular coagulation, was not mentioned. Such patients usually have a high degree of parasitism, are very ill and need intensive supportive care. From the theoretical point of view the initial management should include the rapid elimination of the parasitized red cells and correction of the intravascular coagulation. This can easily be accomplished by large volume whole blood exchanges using heparinized blood[2-4] and has resulted in dramatic recovery of at least one such patient with severe blackwater fever.

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REFERENCES

1. Fitzgerald FT: Malaria: A modern dilemma—University of California, San Francisco, and San Francisco General Hospital (Clinical Conference). West J Med 1982 Mar; 136:220-226
2. Gyr K, Speck B, Hitz R, et al: Zerebrale Malaria tropica mit Schwarzwasserfieber Schweiz Med Wochenschr 1974 Nov 9; 104 (45):1628-1630 (Eng. Abstr.)
3. Roncoroni AJ, Martino OA: Therapeutic use of exchange transfusion in malaria. Am J Trop Hyg 1979; 28:440-444
4. Nielsen RL, Kohler RB, Chin W, et al: The use of exchange transfusions: A potentially useful adjunct in the treatment of fulminant falciparum malaria. Am J Med Sci 1979; 277:325-329

Correction: Vasopressin Infusions in Bleeding Varices

TO THE EDITOR: Your readers should be notified of a potentially serious error in the editorial on management of bleeding esophageal varices in the February 1982 issue.[1] In the fourth paragraph on page 143, vasopressin infusions should be prepared with 10 ampules of 20 U (not "200 U") vasopressin in 500 ml of 5 percent dextrose solution to make a final concentration of 0.4 units per ml.

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REFERENCE

1. Malt RA: Management of bleeding esophageal varices (Editorial). West J Med 1982 Feb; 136:143-145

* * *

Dr. Malt Replies

TO THE EDITOR: Dr. Adler is quite correct. Fortunately, vasopressin is available only in ampules of 20 U each, as far as I know, so no one is likely to be hurt by my error.

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Probability of Coronary Heart Disease Developing

TO THE EDITOR: Review of Erica Brittain's chart on the probability of coronary heart disease in men (in her January article[1]) shows a fall in probability from ages 65 to 70 in those with a cholesterol level of 225 through 315 mg per dl and more surprisingly a fall in probability from those with a cholesterol level under 255 to those over 255 mg per dl (in those age 70). I presume this is an error. A correction or explanation would be appreciated.

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REFERENCE

1. Brittain E: Probability of coronary heart disease developing (Information). West J Med 1982 Jan; 136:86-89

* * *

Ms. Brittain Replies

TO THE EDITOR: *Given the mathematical model* on which these charts (and the *Coronary Risk Handbook*[1]) are completely based, the probabilities in question are correct. The Framingham Study investigators judged this model to have an excellent fit to their data. The model includes a negative age by serum cholesterol interaction term which is responsible for the surprisingly low coronary heart disease (CHD) risk when *both* cholesterol and age are high. This reflects the finding that cholesterol is a strong coronary risk factor

among middle-aged men, but does not appear to be a risk factor for men aged 65 or greater.

Therefore, a 55-year-old man with a very high cholesterol level has a high risk of CHD developing. However, a 70-year-old man whose cholesterol level is high has no greater risk than if he had very low cholesterol and consequently his risk is less than the younger man's.

But why does the risk in 70-year-old men *decline* with rising cholesterol values? The decline is negligible: consider a 70-year-old man with systolic blood pressure of 150 and absence of smoking habit, left ventricular hypertrophy (LVH) and glucose intolerance—if his cholesterol level were 165 mg per dl his precise risk *based on the model* would be .089, but if his cholesterol level were 315 his risk would be .082. Perhaps the coronary risk is actually unchanged by cholesterol level at this age; the small decline in risk exhibited by the charts may simply be due to the associated model's good fit over all and is merely a statistical fluke. However, an argument that the decline is not an artifact can be made. Men with elevated cholesterol levels who survive to age 70 may tend to be protected against CHD by some unknown factor, and thus because of this protection they may be at lower risk for CHD than 70 year olds with low cholesterol.

In the *Coronary Risk Handbook* the same surprising relationships may be observed. For example: Age-55, SBP-150, cholesterol-355, absence of smoking habit, LVH and glucose intolerance yields a risk of .138 (page 16). The same values except age-65, yield a risk of .111 (page 20).

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REFERENCE

1. Coronary Risk Handbook—Estimating Risk of Coronary Heart Disease in Practice. New York, American Heart Association, 1973

Low Anion Gap and Hyponatremia

TO THE EDITOR: A decreased anion gap has previously been described in association with hyponatremia.[1] The proposed causes for the low anion gap in hyponatremia are dilution of extracellular fluid and increased losses of phosphate and sulfate. It has also been suggested that the anion gap would be useful in distinguishing hyponatremia in volume-expanded states from other hyponatremic states.[2] This is based on the fact that hyponatremia associated with volume expansion would feature increased urinary excretion of unmeasured anions, while this would not be expected to occur in volume-depletion hyponatremia. To investigate this further, I studied patients who had hyponatremia either at admission or in whom it developed after admission to hospital.

TABLE 1.—*Changes in Various Biochemical Measurements Occurring With the Decrease in Serum Sodium*

Serum Chemistries	*Change in Concentration (Mean±SD)*	*Change Using Mean±SD of Previous Measurement as Baseline (percent)*
Anion gap (N=22)	−3.6±2.1 mEq/liter	−20.2
Sodium (N=22)	−12.8±5.0 mEq/liter	− 9.3
Chloride (N=22)	− 9.2±6.0 mEq/liter	− 9.6
Potassium (N=22)	− 0.1±0.9 mEq/liter	− 2.3
Total CO_2 (N=22)	− 0.5±1.5 mEq/liter	− 1.7
Phosphate (N=12)	− 0.2±0.07 mg/dl	− 6.0
Calcium (N=12)	− 0.7±0.08 mg/dl	− 7.7
Magnesium (N=12)	− 0.1±0.04 mg/dl	− 4.0
Albumin (N=14)	− 0.3±0.09 grams/dl	−11.0
Creatinine (N=22)	− 0.1±0.05 mg/dl	+11.0

CO_2=carbon dioxide; (−) represents decrease in concentration and percentage.

Charts of 24 patients with hyponatremia who had 58 measurements of serum electrolytes were reviewed. All patients had serum creatinine values of less than 2 mg per dl and normal values of "corrected" serum calcium, magnesium, phosphate and total carbon dioxide (CO_2). None of the patients had a serum albumin of less than 3.0 grams per dl or a gamma-globulin level of greater than 1.6 grams per dl. Of the 24 patients (group A), 12 fell into the category of syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The other 12 patients (group B) included six with liver disease (no ascites) and five with mild congestive heart failure (no edema). None of these patients had any clinical evidence of volume depletion. Mean plasma lactate in six patients in group B was 1.3 mmol per liter. The mean ±SD of the anion gap (which was calculated as sodium + potassium − chloride + bicarbonate radical [$Na+K-Cl+HCO_3$]) was calculated (1) for both groups A and B and (2) in patients with serum sodium less than and greater than 120 mEq per liter. In those 22 patients who had serial measurements of electrolytes, the decrease in serum sodium was correlated with the change in the anion gap. The percentage change in the anion gap from the original baseline value was calculated for each patient. Changes in serum phosphate, calcium, magnesium, albumin and creatinine were also calculated in those patients in whom these measurements were available.

The mean ±SD of the anion gap in group A (30 measurements) was 12.3±2.9 mEq per liter. It was 12.6±3.2 mEq per liter in group B (28 measurements). There was no significant difference between the two groups. The anion gap was lower when the serum sodium was less than 120 mEq per liter (mean±SD is 11.3±2.1 mEq per liter, N=24) compared with when it was greater than 120 mEq per liter (mean±SD is 13.4±1.9 mEq per liter, N=34) ($P<.02$). Values of the anion gap in all groups are lower ($P<.01$) compared with the normal anion gap in 100 controls studied at this hospital[3] (mean±SD is 15.2±1.6 mEq per liter).

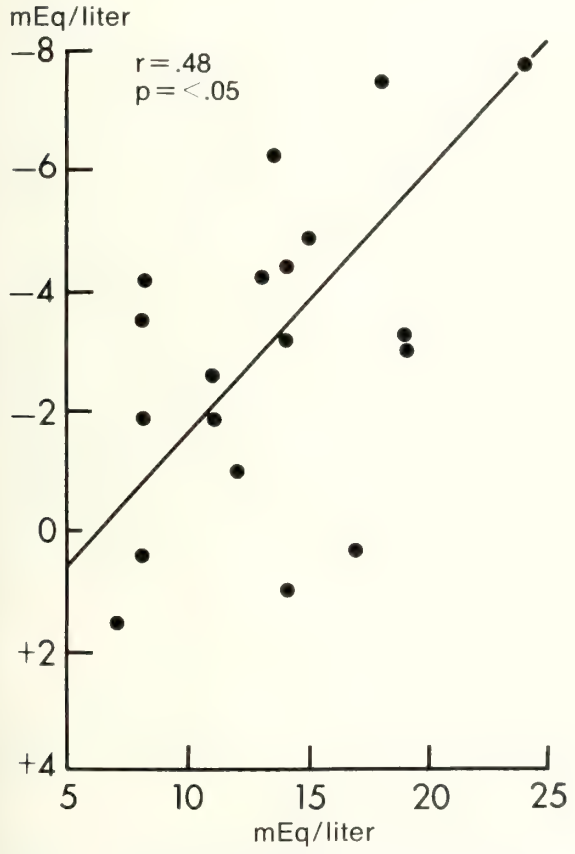

Figure 1.—Correlation between the decrease in serum sodium and change in the anion gap. Na=sodium.

I have determined that the current mean has not changed from the previous normal mean. The changes in the various biochemical measurements in the patients with hyponatremia are summarized in Table 1. The mean percentage decrease in the anion gap (20.2) is twice greater than what can be expected by dilution alone (9.3). Changes in unmeasured anions and cations virtually cancel each other out and do not account for the remainder of the decrease in the anion gap. Although serum sulfate and organic acids were not measured, it is unlikely that significant changes occurred in these parameters. Absence of a change in total CO_2 excluded the role of a resolving acidosis in decreasing the anion gap. Because our methods for measuring electrolytes are linear beyond the concentrations measured, an analytical cause for the decrease in the anion gap can be excluded. A positive correlation (Figure 1) ($r=.48$, $P<.05$) obtained between the decrease in the anion gap and the serum sodium suggests that an authentic relationship exists between them. Because plasma proteins account for about two thirds of the normal anion gap,[4] changes in net negative protein charge could occur in hyponatremia. There is no experimental evidence to support this hypothesis, however, and it deserves further study. The present study also shows that the anion gap does not distinguish hyponatremia due to extracellular fluid overload from other causes of hyponatremia.

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REFERENCES

1. Fischer MD, Rector FC: Decreased anion gap and hyponatremia (Correspondence). N Engl J Med 1978 Jan 12; 298:111
2. Oh MS, Carroll HG: Decreased anion gap and hyponatremia (Correspondence). N Engl J Med 1978 Jan 12; 298:111-112
3. Frohlich J, Adam W, Golbey MJ, et al: Decreased anion gap associated with monoclonal and pseudomonoclonal gammopathy. Can Med Assoc J 1976 Feb 7; 114:231-232
4. Emmett ME, Narins RG: Clinical use of the anion gap. Medicine (Baltimore) 1977 Jan; 56:38-54

Topics in
Primary Care Medicine

Refer to: Lo B: The diagnosis of pulmonary embolus (Topics in Primary Care Medicine). West J Med 1982 Jun; 136: 542-545

The Diagnosis of Pulmonary Embolus

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In this issue The Western Journal of Medicine *begins a new series, "Topics in Primary Care Medicine," that will present articles on common diagnostic or therapeutic problems encountered in primary care practice. These articles will address such frequently occurring problems as dizziness, pruritus, insomnia, shoulder pain and urinary tract infections. These problems usually do not fall into well-defined subspecialty areas and are rarely discussed thoroughly in medical school, house staff training, textbooks and journals. Often the pathophysiology is poorly understood and clinical trials to assess the effectiveness of diagnostic tests or therapies are often lacking. Nevertheless, these problems confront practitioners with practical management questions.*

The articles in this series will discuss new tests and therapies and suggest a reasonable approach even when definitive studies are not available. Each article will have several general references for suggested further reading. We hope this new series will be of interest and we welcome comments, criticisms and suggestions.

—BERNARD LO, MD
—STEPHEN J. McPHEE, MD
Series' Editors

THE DIAGNOSIS of pulmonary embolism (PE) is a common, important and difficult problem for primary care physicians. It is important not to miss the diagnosis inasmuch as the mortality of untreated PE is 25 percent, compared with a mortality of 2 percent to 9 percent in patients treated with heparin.

Establishing the diagnosis of PE can be difficult. Findings on history, physical examination and laboratory tests are not specific. The results of lung scanning may not be conclusive. Angiography provides definitive diagnosis but is invasive and costly.

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Supported in part by the Robert Wood Johnson Foundation and the John A. Hartford Foundation.

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Because PE is a serious disease with nonspecific presentations, the physician must consider the diagnosis and work up many patients who in fact do not have PE. In a prospective multicenter study, over 94 percent of patients suspected of having PE were found not to have it. PE should be efficiently ruled out in these patients. Falsely positive diagnoses have serious consequences because the risk of major bleeding from heparin is as high as 8 percent and from warfarin, 17 percent.

Clinical Evaluation

The clinical presentation of PE is varied and not specific (Table 1). Predisposing factors include deep venous thrombosis, embolization, chronic pulmonary or cardiac disease, estrogen use or pregnancy and cancer. The most common

ABBREVIATIONS USED IN TEXT

COPD = chronic obstructive pulmonary disease
PE = pulmonary embolism
P_{O_2} = oxygen partial pressure
V/Q = ventilation-perfusion

symptoms are dyspnea, pleuritic pain and cough. In patients with prior cardiac or pulmonary disease, a large pulmonary embolus may cause shock and congestive heart failure. More subtle presentations include worsening of heart failure or onset of atrial fibrillation.

Tachypnea is a common finding on physical examination. Tachycardia, increased second pulmonic heart sound, fever, deep venous thrombosis and pleural rub are less frequently found.

Laboratory Studies

Hypoxemia occurs in 88 percent of cases. Abnormalities in lactate dehydrogenase (LDH), serum aspartate aminotransferase (formerly glutamic-oxaloacetic transaminase, SGOT) and bilirubin usually are not helpful in establishing the diagnosis. Although the chest x-ray studies are abnormal in 50 percent to 88 percent of cases, the findings of effusion, atelectasis, infiltration and an elevated hemidiaphragm are not specific. Similarly, though the electrocardiogram is abnormal in 87 percent of cases, the findings of tachycardia and ST segment changes are not specific. Acute cor pulmonale, said to be diagnostic of PE, is found in only 26 percent of cases.

A normal result on a sensitive* test when the clinical suspicion is low helps rule out the diagnosis. For example, in a young woman with tachypnea and anxiety but no risk factors, the likelihood of PE certainly is no greater than the 6 percent prevalence in the multicenter study. If she has an oxygen partial pressure (P_{O_2}) greater than 80 mm of mercury, this probability is reduced to 2 percent. In another patient where the clinical suspicion of PE is higher (for example, if the prior probability is estimated to be 25 percent), a P_{O_2} greater than 80 mm of mercury reduces the probability of PE to 10 percent.

But abnormal results of sensitive tests do not establish the diagnosis of PE. Because these tests are not specific,† further evaluation is needed. Specificity has not been rigorously studied; Table 1 lists reasonable estimates. For example, the only reported specificity for hypoxemia is 34 percent.

*The sensitivity of a test is the probability of having a positive result in a patient with the disease.

†The specificity of a test is the probability of having a negative result in a patient who does not have the disease.

TABLE 1.—*Sensitivity and Specificity of Findings in Pulmonary Embolism*

Findings	*Sensitivity (percent)*	*Specificity (percent)*
Symptoms		
Dyspnea	70-84	<50
Pleuritic pain	42-74	50-75
Cough	42-53	50-70
Hemoptysis	14-30	50-70
Predisposing factors	94	50-70
Physical findings		
Tachypnea >24	37-92	50-70
Tachycardia >90	44-53	50-70
Increased P_2	53	50-70
Fever	43-50	50-70
Deep venous thrombosis	30-33	50-70
Pleural rub	14	50-70
Laboratory tests		
P_{O_2} <80 mmHg	88	<50
Abnormal chest x-ray	50-80	<50
Abnormal electrocardiogram	87	<50
Lung scanning		
Abnormal perfusion scan	99	<50
Abnormal V/Q scan	36-99	73-98*
Abnormal angiogram	98	>99

P_2 = pulmonic second sound; P_{O_2} = oxygen partial pressure; V/Q = ventilation perfusion

*Depends on the pattern of abnormality.

Lung Scan

Lung scanning is usually the next step after clinical evaluation and simple laboratory tests. In a perfusion scan, images are taken after the injection of technetium-labeled albumin. Defects represent areas of decreased perfusion. In a ventilation scan, images are taken after inhalation of xenon or krypton. Defects represent areas of decreased ventilation. A ventilation-perfusion (V/Q) scan compares ventilation images with perfusion images.

The diagnostic accuracy of lung scans, however, is controversial. All reported series suffer from selection bias because not all patients having scans also have pulmonary angiograms to confirm the diagnosis. Observers differ substantially in interpreting scans. In one series, five experts could agree on the classification of perfusion scans into four categories in only 40 percent of cases. Interobserver agreement on V/Q scans has not been studied.

Perfusion scans are highly sensitive for PE (Table 1), so that *a normal perfusion scan effectively rules out the diagnosis.* Furthermore, if a scan shows multiple subsegmental perfusion de-

fects, there is a low (7 percent to 9 percent) probability of finding PE on angiography. However, other abnormal findings on perfusion scans are not specific for PE and must be evaluated further.

V/Q scans increase the diagnostic accuracy of abnormal perfusion scans in some groups of patients. Patients with multiple large perfusion defects unmatched by ventilation defects have a high probability of having PE on angiography. If the perfusion defects are lobar, the probability of PE is 92 percent to 100 percent. If the defects are segmental, the probability of having PE is 85 percent to 95 percent. On the other hand, patients with single or multiple perfusion defects that are matched by ventilation defects have a low (0 percent to 9 percent) probability of having PE on angiography. Angiography usually is not necessary in these high and low probability groups of patients.

Difficulties With Lung Scans

The accuracy of scans with defects corresponding to infiltrates on x-ray is controversial. One series suggests that if the perfusion defects are larger than the x-ray infiltrates, the probability of PE is high, whereas if they are smaller, the probability is low. However, the series is small and interpretations of "greater" and "smaller" may be unreliable. A prudent course is to obtain angiograms in these patients.

Other findings on V/Q scan have an intermediate (20 percent to 40 percent) probability of PE. Examples are diffuse ventilation abnormalities due to chronic obstructive pulmonary disease (COPD) and scans with multiple perfusion defects, some matched by ventilation defects and others unmatched. This intermediate probability group requires angiography to confirm or exclude the diagnosis.

In some circumstances the physician may decide to omit lung scans and to proceed directly to angiography after clinical evaluation. Examples are patients with COPD or radiographic infiltrates who are suspected of having PE.

Technical details may influence the ordering of scans. Some centers recommend initially ordering a V/Q scan rather than a perfusion scan because a high-quality xenon ventilation scan cannot be obtained for several hours after a perfusion scan. If the clinical suspicion of PE is low, however, it is reasonable to order a perfusion scan alone as a first step. If it is negative, the patient is spared an unnecessary procedure. If the perfusion scan does not rule out PE, heparin can be given until more definitive diagnosis with ventilation scan or angiogram is obtained. It is claimed that krypton ventilation scans may solve this problem because they have high resolution even if done immediately after perfusion scans. However, krypton is more expensive, not widely available and not rigorously studied.

Pulmonary Angiography

Angiography is considered the "gold standard" for definitive diagnosis of PE. It is highly specific and sensitive (Table 1). Intraluminal filling defects are diagnostic of PE and a negative angiogram rules it out. However, falsely negative angiograms may occur, as 1.5 percent to 2.5 percent of patients with negative angiograms will have later angiographic or autopsy evidence of PE. Falsely negative angiograms due to resolution of the embolus are rare if the test is done within 48 hours of the onset of symptoms. The interobserver reliability of angiogram readings is excellent, with disagreement in fewer than 6 percent of cases.

Although angiography provides definitive diagnosis, it is impractical to do angiograms on all patients suspected of PE. Most angiograms would be negative because PE is overdiagnosed clinically. High quality studies cannot be obtained at all hospitals. Moreover, angiograms are expensive, costing from $500 to $1,000 depending on the number of films taken, compared with $175 for a V/Q scan.

Angiograms also involve some risk to patients. The mortality of angiography is under 0.5 percent, with intractable shock in patients who have elevated right heart pressures accounting for many deaths. Significant morbidity, such as cardiac arrest, symptomatic arrhythmias, right ventricular perforation and anaphylaxis, occur in 1.6 percent to 2.3 percent of cases. These data were gathered at centers doing more than 80 procedures a year; the complication rate at less experienced centers probably is higher.

Individualizing the Workup

The workup for PE must be specific for each patient. In a particular hospital, some tests may not be available or local experience may not match the results reported in the literature. Also the values of the physician and patient, especially

their attitudes toward risk and uncertainty, must be taken into account. In many circumstances a 90 percent probability of PE may be sufficient reason to begin therapy. In the following situations, however, the physician or patient may desire the greater diagnostic certainty that angiography offers compared with lung scanning: (1) The patient is at high risk for bleeding from anticoagulation because of advanced age, recent surgical procedures, trauma or bleeding or hemostatic defects. (2) Thrombolytic therapy, which increases the risk of major bleeding, is considered. Angiography should be done via an antecubital rather than a femoral approach, so that bleeding at the site can be controlled by direct pressure. (3) Interruption of the inferior vena cava is considered.

New Approaches

One suggested approach to diagnosing PE is to study the legs with venography or impedance plethysmography and to initiate anticoagulation if deep venous thrombosis is present, even though the presence of PE may be uncertain. However, the incidence of false-negative diagnoses with this approach has not been studied rigorously. Another approach is to measure fibrin and fibrinogen degradation products or platelet release factors. Again, this approach has not been rigorously studied.

Summary

Clinical findings and simple laboratory tests can suggest PE, but positive findings must be confirmed. A normal perfusion scan effectively rules out PE. Multiple lobar or segmental V/Q mismatches have a high probability of PE, but matched ventilation and perfusion defect(s) have a low probability of PE. Arteriography will be necessary with other V/Q scan results or when greater diagnostic certainty is desired. Treatment must be individually tailored according to the details of the case, the availability of tests and the values of the patient and physician.

GENERAL REFERENCES

Bell WR, Simon TL, DeMets DL: The clinical features of submassive and massive pulmonary emboli. Am J Med 1977 Mar; 62:355-360
Review of clinical presentation of PE.

Cheely R, McCartney WH, Perry JR, et al: The role of noninvasive tests versus pulmonary angiography in the diagnosis of pulmonary embolism. Am J Med 1981; 70:17-22

Griner PF, Mayewski RJ, Mushlin AI, et al: Selection and interpretation of diagnostic tests and procedures. Ann Intern Med 1981; 94(4, Part 2):553-600
Discusses sensitivity, specificity and predictive value of tests, with application to the diagnosis of PE.

McNeil BJ: Ventilation-perfusion studies and the diagnosis of pulmonary embolism. J Nucl Med 1980 Apr; 21:319-323
Two clinical series on the uses and limitation of lung scans.

A National Cooperative Study: The urokinase pulmonary embolism trial. Circulation 1973; 47(Suppl II):29-108.
The results of a well-designed study on thrombolytic therapy. Also excellent data on the clinical presentation of PE.

Robin ED: Overdiagnosis and overtreatment of pulmonary embolism: The emperor may have no clothes. Ann Intern Med 1977 Dec; 87:775-781
Critique of lung scans in diagnosis of PE.

Thrombolytic therapy in thrombosis: A National Institutes of Health consensus development conference. Ann Intern Med 1980 Jul; 93:141-144

Special Essay

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Holistic Medicine: Advances and Shortcomings

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Holistic medicine is an attitudinal approach to health care rather than a particular set of techniques. It addresses the psychological, familial, societal, ethical and spiritual as well as biological dimensions of health and illness. The holistic approach emphasizes the uniqueness of each patient, the mutuality of the doctor-patient relationship, each person's responsibility for his or her own health care and society's responsibility for the promotion of health.

As holism has become an increasingly popular concept, it has been distorted by both proponents and critics. Tendencies to equate holism with particular therapeutic modalities, to neglect public health for a one-sided emphasis on individual responsibility and to reject rather than elaborate on the scientific method have hampered the movement's progress. In the future orthodox and alternative approaches and techniques must all be seen as complementary parts of a larger synthesis that will genuinely deserve the name of holism.

IN THE PAST DECADE holistic medicine has rapidly emerged as a visible and controversial force in American medicine. The American Holistic Medical Association, founded three years ago, now claims some 500 physician members and has established a working alliance with the American Medical Students Association. Approximately 150 holistic health centers[1] have opened in all parts of the country and each month workshops and conferences on the holistic approach to health care draw thousands of physicians, other health care professionals and consumers. Several dozen medical schools offer electives in holistic and "alternative" medicine, and each semester faculty interest and student demand are generating others.

Holistic medicine has often been misunderstood and caricatured by its medical critics. Though statements by some of its advocates may make it appear so, holistic medicine is not merely a collection of obscure and unproved modalities and ancient truisms,[2] nor is it simply a derivative of "eclectically oriented psychotherapies."[3] Holistic medicine is not an anti-intellectual attempt to purge health care of qualified physicians or accepted biomedical therapeutics,[4] to deny the social and economic antecedents of illness[5] or to blame those who are sick for their own misfortune.[6] Holistic medicine may, in fact, be an important force in a broader effort to create a contemporary synthesis, one potentially richer than the biomedical and empiric traditions of which it is compounded.

It seems appropriate, as holistic medicine gains greater currency and as the conflicts it generates escalate, to offer a brief and, it is hoped, demystifying summary of its salient characteristics, to

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highlight the attitudes and practices that inhibit its fruitful elaboration and to provide the foundation for a bridge to mainstream medical theory and practice.

Holistic medicine derives its name from biologist-philosopher Jan Christian Smuts's 1926 book *Holism and Evolution.*[7] To Smuts, holism (from the Greek *holos*) was an antidote to the analytic reductionism of contemporary science. It was a way of comprehending whole organisms and systems as entities greater than and different from the sum of their parts. Though it has sometimes been contrasted with them, holistic medicine includes *humanistic medicine* (which emphasizes the relationship between and personal development of both physician and patient), *psychosomatic medicine* (which is concerned with the interdependence and mutual influence of psychological and physical factors) and *behavioral medicine* (which stresses the psychosocial causes and effects of illness). Rightly understood and practiced, it is a comprehensive approach, not a smorgasbord of techniques, a force for reconciliation rather than division.

Holism has, of course, always been integral to healing. Hippocrates and the tradition out of which modern biomedicine has grown emphasized the environmental causes and treatment of illness; the etiologic and therapeutic importance of psychological factors, nutrition and life-style; the interdependence of mind, body and spirit, and the need for harmony between an individual and his social milieu and natural enviroment.[8,9] Holism is now invoked (at times too stridently) to balance more recent, technologically influenced tendencies to equate health care with the pharmacologic and surgical treatment of specific disease entities. Too often those who champion technology in the service of medical progress ignore the shaping force of interpersonal, social and economic factors on health and disease, confusing, in Sir William Osler's words, "the patient with his illness."

The origins of holistic medicine in our present "crisis" in health care have been described in great detail elsewhere.[10] Suffice it to say that the concept of holistic medicine has arisen at a time when the burden of disease in the United States has shifted from acute to chronic illness and when rising costs and proliferating side effects are raising questions even about our successful treatments. We are in a scientific climate that challenges conventional pre-einsteinian categories of cause and effect, a cultural context in which the fragmentation, dehumanization and enforced passivity of human services—and indeed of life itself—are of enormous professional and public concern.

Characteristics of Holistic Medicine

The cornerstone of holistic medicine is its insistence that each patient be understood and treated as a unique individual made up of body, mind and spirit and that any health care must also take into account a person's environment.[10] Holism offers its adherents a basis for overcoming the fragmentation of specialization by recalling the responsibility for psychological, spiritual and social therapies from the specialists—in internal medicine, mental health, pastoral counseling and social welfare—to whom they have been parceled out and reuniting those responsibilities in each practitioner and in teams of health care workers. Practitioners should include a patient's family, community and cultural background in the field of diagnostic evaluation. They must explore and appreciate the minute particularity of the new world that each patient brings to them and become sensitive to the complex psychology and uncommon life of people with common illnesses.

A holistic perspective respects the ways family and culture shape pathophysiology and distinguishes between the anatomic lesions that constitute a disease state or diagnostic category and an individual's experience of illness.[11] This perspective leads to a recognition of culturally sanctioned views of illness and medical care and to the incorporation of indigenous healers where their services are appropriate. Such a perspective also provides a theoretic basis for including nuclear and extended families and communities in the treatment of conditions as varied as hypertension,[12] cancer,[13] chronic pain[14] and schizophrenia.[15]

Proponents of holistic medicine suggest that patients with identical diagnoses may require quite different approaches—that is, different forms of exercise and diet and of pharmacologic and psychotherapeutic intervention. For example, one depressed asthmatic adolescent may best be treated in a group that runs several miles a day, while another obtains greater benefit from a systems-oriented family therapy.[16,17] One may do well with dietary manipulation, while the other continues to require pharmacologic intervention.

This aspect of holism is largely unexceptionable. A number of contemporary theoreticians, including Engel[18,19] and Eisenberg,[20] have re-

peatedly and cogently argued for adopting a carefully individualized biopsychosocial model of illness and medical care, while other investigators, notably Frank[21] and Schmale,[22] have suggested that such quasi-religious patient attitudes as *faith, hope* and *despair* may be of considerable importance in the course and outcome of an illness.

At times, however, some who describe themselves as holistic have stretched the limits of medical credibility—and common sense—and violated the principles of holism by vigorously championing one aspect of the holistic approach at the expense of others or failing to integrate the services of the various practitioners in a holistic health program. Some have emphasized the importance of life-style, attitude and emotional factors at the expense of necessary pharmacologic or surgical interventions, while others have neglected the psychosocial aspects of health care in an effort to establish the efficacy of a particular and enthusiastically promoted somatic remedy.

Physicians who have disproportionately emphasized the spiritual aspect of the holistic approach are perhaps most vulnerable to these criticisms. The results of controlled laboratory studies of healers by Grad[23] and Smith[24] and investigations of the therapeutic efficacy of placebo[25] and faith[26] suggest that "nonmaterial" forces may produce biochemical changes in living organisms. But aside from anecdotal accounts of so-called miracle cures,[27-29] there is as yet no evidence for the efficacy of "psychic" healing and no justification for its evangelic promotion.

Holistic medicine emphasizes the responsibility each person should assume for his or her health. This emphasis reflects a shift in illness patterns from infectious to chronic stress-related diseases, recent insights into the influence of personal habits and life-style on the origin and outcome of these conditions and the conclusions of such widely read documents as *A New Perspective on the Health of Canadians*[30] and "Doing Better and Feeling Worse."[31] This idea of personal responsibility owes much to nonmedical influences: the *human potential movement* with its focus on the therapeutic role of will and the relationship between improved health and self-actualization[32]; and the revival of the emersonian tradition of self-reliance in an American population that has come to feel itself overly dependent on large institutions and authoritative, if not authoritarian, practitioners.

Some of the technology for implementing self-responsibility has been well developed and well studied. Standardized tests such as the Social Readjustment Rating Scale[33] and the Health Hazards Appraisal[34] have enabled some patients to see how their habits, attitudes and expectations—the way they live and work and think and feel—affect their physical and emotional health. Psychotherapeutic techniques, such as freudian *free association*, jungian *active imagination,* role playing, hypnosis and visualization are also used to help patients become more aware of the ways in which they may have translated psychological processes and interpersonal dynamics into physical symptoms.[35] Though these introspective approaches seem intuitively correct to psychologically minded physicians and patients, they have so far received no systematic confirmation.

Many of the therapeutic approaches that holistic practitioners use also shift the burden of responsibility from physician to patient. In this context, the physician's work is the mobilization of the patient's own capacity for self-regulation, the stimulation of what Hippocrates described as the *vis medicatrix naturae,* the healing force of nature. Inspired by animal experiments on autonomic regulation[36] and the example of Indian yogis,[37] and aided by contemporary instrumentation, they teach their patients to use biofeedback, autogenic training, meditation and self-hypnosis to control blood pressure, slow heart rate and intestinal motility, relieve migraine headaches and chronic pain and alter electroencephalographic patterns that are characteristic of seizure disorders.[38]

Though it is extremely difficult to tease out the specific pathways that mediate these varied approaches, there is little doubt that they increase the level of patient participation, promote a sense of mastery and augment the placebo effect. On occasion, however, these practices have produced side effects of their own. At times, patients' failures to mobilize their own healing forces have produced an attitude of therapeutic nihilism in impatient and arrogant practitioners. Moreover, without a balanced attention to the environmental causes and remedies of some illnesses, the doctrine of individual responsibility can indeed degenerate to "victim blaming."

Holistic medicine includes the promotion of health and the prevention of disease and emphasizes the role of education in the process. Many holistic physicians place *well-being* on a continuum that ascends from clinical disease through

the state of complete physical, mental and social well-being, which the World Health Organization has described as health, to "super health."[39] The latter is a condition of extraordinary vigor, joy and creativity that some regard as the psychobiologic concomitant of self-actualization. This viewpoint encourages physicians to help those who are functioning well to make still greater use of their biopsychosocial potential, as well as to treat clinical illness.

Coupled with the emphasis on individual responsibility and catalyzed by consumer movements in health care, this perspective has contributed to a change in the physician-patient relationship. There is a growing emphasis on the partnership between physician and patient[30] and a corresponding metamorphosis in the physician's role from treater to teacher. Some physicians have supplemented their therapeutic interventions with classes for activated patients,[40] instruction in self-care[41] and group courses on topics like stress reduction, interpersonal relations and nutrition.[42] Many of these classes are conducted jointly by professionals and present and former patients.

At the level of individual care, this evolving perspective and these practices provide a link between medicine and public health. Organizationally, they have contributed to the development of health promotion and "wellness" centers within and outside of traditional health care settings.[1]

Holistic practitioners use a variety of diagnostic and therapeutic measures that lie outside the canon of traditional Western medical practice. Some of these approaches, particularly an expanded attention to the therapeutic and preventive use of nutrition and exercise, reflect the more general professional and public concern with the effects of life-style on health and illness. Here the difference between the holistic and the conventional approach is more a matter of degree and emphasis. Thus a holistic practitioner may be more likely to combine psychotherapy with aerobic exercise, rather than psychoactive drugs, in the treatment of neurotic depression and to investigate the possible influence of mild hypoglycemia, food allergy and caffeine sensitivity, as well as psychogenic factors, on the production of anxiety.

Holistic physicians have also explored the utility of measures that have been found in other cultures and at other times to be empirically useful. This has led to the use of such investigative techniques as iridology, auriculodiagnosis and Chinese pulse-diagnosis[43-45] and such therapeutic modalities as acupuncture, herbalism, homeopathy, fasting and musculoskeletal manipulation singly or in combination with traditional Western allopathic practice. Though this diagnostic and therapeutic flexibility has produced a number of interesting anecdotal accounts,[1,14,46] treatment results have not been systematically investigated. Also, at times open-mindedness has degenerated to promiscuity and experimentalism hardened to dogma.

Some practitioners have freely used approaches —acupuncture is a good example—in which they are inexpert. Others, particularly those who have been impressed by anecdotal reports or initial successes, have eschewed the essence of the holistic approach and tried to fit their patients' ills to the procrustean bed of particular diagnostic or therapeutic approaches. A recent study[47] describing the failure of iridology as a diagnostic tool, though unreplicated, demonstrates the importance of scientific evaluation of each of these procedures and the possible dangers of using them in isolation from more conventional approaches.

Holistic medicine emphasizes the potential therapeutic value of the setting in which health care takes place and of the psychosocial supports it makes available. Even the most progressive hospital tends to overwhelm and intimidate, to erect a barrier between those who come for help and those who provide it and to encourage patients to assume and maintain a "sick role."[48] Recent accounts in the literature describe possible ways of mitigating some of the adverse medical and psychological consequences of institutional treatment by actively involving patients in their own care[49] and by providing warm and supportive helpers for those who are hospitalized.[50]

Holistic physicians have tended to advocate change in the locus of care as well as a refinement in care in conventional settings. They do not deny the utility of the hospital in acute life-threatening illness and in high-risk deliveries. They do maintain that birth and death, the treatment of chronic illness, checkups and counseling, which do not require high technology, should be removed from institutional settings. Those who seek help for illness should have the opportunity to participate actively in their own care, in the care of others and in the creation, with professionals, of new kinds of therapeutic settings.

In recent years the holistic perspective has helped to shape the development of centers for general health care,[1,42] treatment of chronic ill-

ness,[51] low-risk deliveries,[52] care of the dying[53] and therapy for psychotic illness.[54] Some of these centers are free standing, others occupy parts of such existing community institutions as churches or schools. Some are residential, others not. Many include home treatment and outreach services. All offer an opportunity for education, socializing and active participation of patients and their families in addition to care in health and illness.

Creating these alternative settings was clearly a necessary step in the development of a holistic approach and provides a locus for innovative practice and continuing delivery of service. But it has tended to limit holistic medical services to communities whose residents are both adventurous and wealthy enough to seek out approaches that are largely uncovered by health insurance. It has also helped to isolate holistic practitioners from more established medical institutions where their work could be informed, challenged and enriched. Efforts are currently under way to establish holistic medicine and "wellness" programs for a variety of socioeconomic groups and in the context of large medical centers.[1]

An understanding of and a commitment to change those social and economic conditions that perpetuate ill health are an integral part of the holistic approach to medicine and are a necessary counterbalance to its emphasis on individual responsibility. A holistic perspective cannot consider individuals in isolation from their social, economic and ecologic contexts. The treatment of a lead-intoxicated child with chelating agents is clearly doomed to failure unless the child's physical surroundings change; administration of vitamins is absurd in the face of poverty that continues to make proper nutrition impossible and inadequate in a society whose entertainment media daily encourage children to subsist on processed junk foods.

Many holistic practitioners address themselves to these issues through classes in self-help, sponsorship of mutual-help groups and public education programs and public advocacy in their communities. Others continue to restrict their field of attention to their individual patients. In their concern with actual or potential governmental and institutional interference, they have retreated from a commitment to change the social and institutional conditions that inevitably limit the effectiveness of their practice, to a privatism and parochialism that must inevitably be self-defeating.

Holistic medicine is as concerned with changing the attitudes of the physicians who practice medicine as with broadening and enriching medical practice. In much of the ancient world and in many contemporary aboriginal societies, the education of healers is at once technical and sacred.[55,56] Traditionally, a process designed to pare away psychological armor, anxiety, fears and arrogance has accompanied the accumulation of technical knowledge and enabled young practitioners to handle their status as healers with modesty and wisdom. The long hours, low pay, persistent challenges and intermittent abuse of internship and residency are a distant shadow of this kind of training. The personal analysis of a modern psychoanalyst is our closest contemporary analogue.

Though there are no formal schools for holistic health care professionals, many physicians have begun to seek out this kind of psychological refinement and nourishment—in continuing education programs sponsored by such newly formed groups as the American Holistic Medical Association and the Association for Holistic Health, in experiential seminars and retreats on humanistic medicine, in courses in medical ethics and in an ever-increasing variety of psychotherapeutic and meditative techniques. In these contexts some have grown more aware of the intrapsychic and interpersonal barriers that prevent them from providing effective and sensitive care. Many have learned to be less dogmatic with and more generous to their patients and to regard their consultations as an opportunity to learn about their own shortcomings as well as their patients' illnesses. Increasingly they are taking seriously the Hippocratic tradition and its insistence that medicine is a sacred trust as well as a profession.

Conclusion

The holistic approach to medicine and health care is a synthesis of the ecologic sensitivity of ancient healing traditions and the precision of modern science. It uses not only techniques whose effectiveness is extensively documented but also those we are just beginning to explore. In addition it unites our contemporary concern with personal responsibility and spiritual and emotional growth and our urge to democratic cooperation and social and political activism.

As this approach continues to gain adherents, its theoretic perspectives must be carefully elaborated, methods evaluated and shortcomings addressed. A balance must be struck between open-

ness to the unconventional and regulation of unscrupulous practitioners who inevitably flourish at the fringe of medicine and capitalize on the despair of prospective patients. Carefully controlled and replicated studies should be undertaken to determine whether particular diagnostic and therapeutic techniques are effective. Perhaps new conceptual frameworks and new methodologies, which can accommodate variations in individualized treatment and the combined effects of a variety of treatments, will be needed.

At the same time, the holistic medical movement must address itself to its own blind spots, that is, the emphasis on individual responsibility at the expense of therapeutic effort and social concern, the tendency toward faddishness and uncritical embrace of the unconventional and the restriction of the holistic approach to those who can afford it.

It is certainly time to create model holistic programs in a variety of communities and in conventional medical settings, to assess whether a combination of health promotion and public education—of Western and alternative approaches—can meet people's health needs more effectively and less expensively than the present system. Finally, it is most important to understand that holistic medicine is not simply an alternative or the sum of its techniques, but an attitude and an approach that can enrich all aspects of health care.

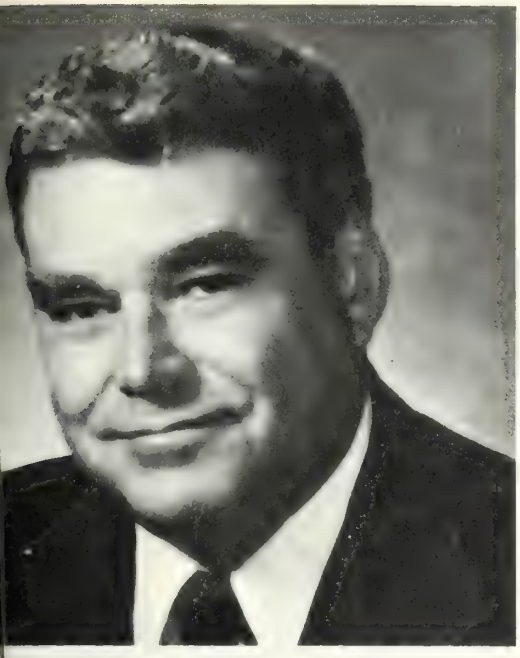
REFERENCES

1. Gordon JS: Holistic health centers, *In* A Hastings, J Fadiman, JS Gordon (Eds): Health for the Whole Person: The Complete Guide to Holistic Medicine. Boulder, CO, Westview Press, 1980, pp 467-482
2. Relmen A: Holistic medicine. N Engl J Med 1979; 300:312-313
3. Yahn G: Impact of holistic medicine, medical groups, and health concepts. JAMA 1979; 242:2202-2205
4. Callan J: Holistic health or holistic hoax. JAMA 1979; 241: 1156
5. Crawford R: You are dangerous to your health: The ideology and politics of victim blaming. Int J Health Serv 1977; 7:663-680
6. Shapiro J, Shapiro D: The psychology of responsibility. N Engl J Med 1979; 301:211-212
7. Smuts JC: Holism and Evolution. New York, Macmillan, 1926
8. Hippocrates: Medical Works, Vol I. WHS Jones, Trans. Cambridge, Harvard University Press, 1923
9. Dubos R: Hippocrates in modern dress, *In* D Sobel (Ed): Ways of Health: Holistic Approaches to Ancient and Contemporary Medicine. New York, Harcourt Brace Jovanovich, 1979, pp 205-220
10. Gordon JS: The paradigm of holistic medicine, *In* A Hastings, J Fadiman, JS Gordon (Eds): Health for the Whole Person: The Complete Guide to Holistic Medicine. Boulder, CO, Westview Press, 1980, pp 3-25
11. Kleinman A, Eisenberg L, Good B: Culture, illness and care: Clinical lessons from anthropologic and cross-cultural research. Ann Intern Med 1978 Feb; 88:251-258
12. Hoebel F: Coronary heart disease and family interaction, *In* P Watzlawick, J Weakland (Eds): The Interactional View: Studies at the Mental Research Institute, Palo Alto. New York, WW Norton, 1976, pp 363-375
13. Simonton OC, Simonton S, Craghton J: Getting Well Again. New York, Tarcher, 1978
14. Bresler DE, Trubo R: Freedom From Pain. New York, Simon & Schuster, 1979
15. Speck RV, Atteneave C: Family Networks. New York, Vantage, 1973
16. Minuchin S, Rosman B, Baker L: Psychosomatic Families: Anorexia Nervosa in Context. Cambridge, Harvard University Press, 1978
17. Greist J, Klein M, Eischen S: Running for treatment of depression. Compr Psychiatry 1979; 20:41-53
18. Engel GL: The need for a new medical model: A challenge to bio-medicine. Science 1977; 196:129-136
19. Engel GL: The clinical application of the biopsychosocial model. Am J Psychiatry 1980 May; 137:535-545
20. Eisenberg L: Psychiatry and society: A sociobiologic synthesis. N Engl J Med 1977 Apr 21; 296:903-910
21. Frank J: Persuasion and Healing: A Comparative Study of Psychotherapy (Rev Ed). Baltimore, The Johns Hopkins University Press, 1973
22. Schmale AH: Giving up as a final common pathway to changes in health. Adv Psychosom Med 1972; 8:20-40
23. Grad B: Some biological effects of the 'laying on of hands': A review of experiments with animals and plants. J Am Soc Psychical Res 1965; 59(2):95-126
24. Smith MJ: Paranormal effects on enzyme activity through laying on of hands. Hum Dimens 1972; 1:15-19
25. Benson H, Epstein M: The placebo effect: A neglected asset in the care of patients. JAMA 1975; 232:1125-1127
26. Frank J: The medical power of faith. Hum Nature, 1978; 1(3):40-47
27. Krippner S, Villoldo A: The Realms of Healing. Millbrae, CA, Celestial Arts, 1976
28. Le Shan L: The Medium, the Mystic, and the Physicist. New York, Viking, 1974
29. Krippner S: Psychic healing, *In* A Hastings, J Fadiman, JS Gordon (Eds): Health for the Whole Person: The Complete Guide to Holistic Medicine. Boulder, CO, Westview Press, 1980, pp 169-177
30. LaLonde M: A New Perspective on the Health of Canadians. Ottawa, Information Canada, 1975
31. Knowles J: Doing better and feeling worse: Health in the United States (Editorial). Daedalus 1977; 106:1
32. Maslow AH: The Farther Reaches of Human Nature. New York, Viking, 1972
33. Holmes T, Rahe R: Social readjustment rating scale. J Psychosom Res 1967; 2:213-218
34. Travis J: Wellness Inventory. Mill Valley, CA, Wellness Center, 1975
35. Jaffe DT: Healing From Within. New York, Knopf, 1980
36. Miller NE, DiCara LV, Solomon H, et al: Learner modification of automatic functions: A review and some new data, *In* TS Barber (Ed): Biofeedback and Self-Control. Chicago, Aldine-Atherton, 1970
37. Green E, Green A: Beyond Biofeedback. New York, Delta, 1979
38. Pelletier K: Mind as Healer, Mind as Slayer. New York, Delta, 1977
39. Carlson R, O'Regan B: The Super Healthy. San Francisco, Institute of Noetic Sciences, 1978
40. Sehnert K, Eisenberg H: How To Be Your Own Doctor—Sometimes. New York, Grossett & Dunlap, 1975
41. Ferguson T: Medical Self-Care: Access to Health Tools. New York, Summit Books, 1979
42. Tubesing DA: Wholistic Health: A Whole Person Approach to Primary Health Care. New York Human Sciences Press, 1978
43. Hastings A: Alternative forms of diagnosis, *In* A Hastings, J Fadiman, JS Gordon (Eds): Health for the Whole Person: The Complete Guide to Holistic Medicine, Boulder, CO, Westview Press, 1980, pp 407-426
44. Bresler DE: Chinese medicine and holistic health, *In* A Hastings, J Fadiman, JS Gordon (Eds): Health for the Whole Person: The Complete Guide to Holistic Medicine. Boulder, CO, Westview Press, 1980, pp 407-426
45. Bresler D, Oleson T, Droening RT: Ear Acupuncture Diagnosis in Musculo-Skeletal Pain. San Francisco, Institute of Noetic Sciences, 1978
46. Oyle I: The Healing Mind. Millbrae, CA, Celestial Arts, 1974
47. Simon A, Worthen DM, Mitas JA: An evaluation of iridology. JAMA 1979 Sep 28; 242:1385-1389
48. Parsons T: The Sick Role, Social Structure and Personality. Glencoe, IL, Free Press, 1963
49. Fiore N: Fighting cancer—One patient's perspective. N Engl J Med 1979 Feb 8; 300:284-289
50. Sosa R, Kennell J, Klaus M, et al: The effect of a supportive companion on perinatal problems, length of labor, and mother-infant interaction. N Engl J Med 1980 Sep 11; 303:597-600
51. Shealy CN: A comprehensive health oriented pain control program, *In* JS Gordon, D Jaffe, DE Bressler (Eds): Mind, Body and Health: Toward an Integral Holistic Medicine. New York, Human Sciences Press, In Press
52. Gordon JS, Haire D: Alternatives in childbirth, *In* A Hastings, J Fadiman, JS Gordon (Eds): Health for the Whole Person: The Complete Guide to Holistic Medicine. Boulder, CO, Westview Press, 1980, pp 303-332
53. Garfield C: Dying and death, *In* A Hastings, J Fadiman, JS Gordon (Eds): Health for the Whole Person: The Complete Guide to Holistic Medicine. Boulder, CO, Westview Press, 1980, pp 379-398
54. Gordon JS: Special study of alternative services, *In* Report to the President of the President's Commission on Mental Health. Washington, DC, Government Printing Office, 1978, pp 376-410
55. Mattson P: Holistic Health in Perspective. San Francisco, Institute of Noetic Sciences, 1978
56. Needleman J: The two sciences of medicine. Parabola 1978; 3:34-35

IDAHO MEDICAL ASSOCIATION

90th Annual Meeting

July 28-31, 1982 • Sun Valley, Idaho



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Clayton C. Morgan, MD
President
Idaho Medical Association

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n Valley—July 28-31, 1982

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IDAHO MEDICAL ASSOCIATION

90th Annual Meeting

JULY 28-31, 1982

WEDNESDAY, July 28, 1982

8:30 am-
5:00 pm HOUSE OF DELEGATES

THURSDAY, July 29, 1982

EXERCISE—PROS AND CONS

8:30 am Introduction
Theodore A. Walters, MD, Chairman
IMA Program Committee

8:45 am What Do We Now Know About Exercise?
William L. Haskell, PhD

9:30 am How to Exercise
Joan Sullivan

10:45 am Dying Young as Late as Possible
Joseph B. Trainer, MD

11:30 am Designing Exercise Shoes
Tim Renn, Nike, Inc.

2:00 pm How Much Exercise Is Enough?
William L. Haskell, PhD

2:45 pm A Rocking Chair Isn't Enough Exercise
Joseph B. Trainer, MD

4:00 pm Panel Discussion

FRIDAY, July 30, 1982

8:30 am Exercise and Aerobics
Joan Sullivan

9:15 am Eat More Weigh Less Diet
William L. Haskell, PhD

10:30 am You're Not Getting Older, You're Getting Better
Joseph B. Trainer, MD

11:15 am Panel Discussion

SATURDAY, July 31, 1982

8:30 am Closing Session, House of Delegates

REGISTRATION FEE $125 FOR NON-IMA MEMBERS AND OUT-OF-STATE PHYSICIANS.

For information contact:

IDAHO MEDICAL ASSOCIATION
P.O. BOX 2668
BOISE, IDAHO 83701 TELEPHONE: (208) 344-7888

William L. Haskell, PhD
Clinical Associate Professor of Medicine, Stanford University School of Medicine and Co-Director, Stanford Cardiac Rehabilitation Program, Palo Alto, California

Joseph B. Trainer, MD
Clinical Professor of Preventive Medicine and Public Health, School of Medicine, The Oregon Health Sciences University, Portland

Joan Sullivan
Instructor Physical Fitness, Portland Community College, and Consultant, President's Council on Physical Fitness and Sports

in memoriam

California Medical Association

ATKINSON, VERNON R., Santa Cruz. Died January 30, 1982, in Santa Cruz, aged 47. Graduate of the St. Louis University School of Medicine, 1964. Licensed in California in 1965. Dr. Atkinson was a member of the Santa Cruz County Medical Society.

BARKER, ROBERT C., Modesto. Died October 1, 1981, in Modesto of heart disease, aged 68. Graduate of the University of California Medical School, Berkeley-San Francisco, 1940. Licensed in California in 1940. Dr. Barker was a retired member of the Stanislaus Medical Society.

BLACK, HARVEY S., Los Angeles. Died February 5, 1982, aged 53. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1961. Licensed in California in 1962. MD degree from California College of Medicine, 1962. Dr. Black was a member of the Los Angeles County Medical Association.

BLEIFER, DANIEL J., Beverly Hills. Died July 5, 1981, aged 53. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1951. Licensed in California in 1951. Dr. Bleifer was a member of the Los Angeles County Medical Association.

CARSEN, ALBERT JOSEPH, San Jose. Died February 10, 1982, in San Mateo of myocardial infarction, aged 67. Graduate of the University of Toronto Faculty of Medicine, 1938. Licensed in California in 1943. Dr. Carsen was a member of the Santa Clara County Medical Society.

DUNPHY, J. ENGLEBERT, San Francisco. Died December 25, 1981, in San Francisco of cancer, aged 73. Graduate of Harvard Medical School, Boston, 1933. Licensed in California in 1964. Dr. Dunphy was a member of the San Francisco Medical Society.

EICHORN, KARL B., San Francisco. Died February 1, 1982, in San Rafael, aged 80. Graduate of the University of California Medical School, Berkeley-San Francisco, 1937. Licensed in California in 1937. Dr. Eichorn was a retired member of the San Francisco Medical Society.

FEDER, BERNARD H., Rancho Palo Verdes. Died November 26, 1981, aged 64. Graduate of the University of Southern California School of Medicine, Los Angeles, 1940. Licensed in California in 1940. Dr. Feder was a retired member of the Los Angeles County Medical Association.

HARRIS, CHARLES R., Richmond. Died February 12, 1982, aged 60. Graduate of Baylor University College of Medicine, Houston, 1950. Licensed in California in 1957. Dr. Harris was a member of the Alameda-Contra Costa Medical Association.

HENKE, HAROLD E., Duarte. Died January 12, 1982, aged 85. Graduate of Rush Medical College, Chicago, 1925. Licensed in California in 1949. Dr. Henke was a member of the Los Angeles County Medical Association.

HOFFMAN, RALPH L., San Diego. Died December 15, 1981, aged 72. Graduate of the University of Michigan Medical School, Ann Arbor, 1932. Licensed in California in 1934. Dr. Hoffman was a retired member of the San Diego County Medical Society.

LIGHT, LOUISE E., Los Angeles. Died February 18, 1982, aged 73. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1938. Licensed in California in 1938. MD degree from California College of Medicine, 1962. Dr. Light was a member of the Los Angeles County Medical Association.

LYNCH, JAMES M., Escondido. Died February 20, 1982, aged 81. Graduate of the Yale University School of Medicine, New Haven, 1930. Licensed in California in 1938. Dr. Lynch was a retired member of the San Diego County Medical Society.

OPACITY, ERNEST A., Vista. Died February 16, 1982, in Vista, aged 74. Graduate of Medizinische Fakultät der Universität, Wien, 1936. Licensed in California in 1943. Dr. Opacity was a retired member of the San Diego County Medical Society.

RICHARDS, MELVIN R., Santa Monica. Died January 12, 1982, aged 56. Graduate of the University of Utah College of Medicine, Salt Lake City, 1947. Licensed in California in 1955. Dr. Richards was a member of the Los Angeles County Medical Association.

SAUER, FRANK J., Laguna Hills. Died August 9, 1981, aged 91. Graduate of the University of Illinois College of Medicine, Chicago, 1917. Licensed in California in 1921. Dr. Sauer was a member of the Los Angeles County Medical Association.

STARR, MERRITT P., Claremont. Died February 9, 1982, aged 88. Graduate of Rush Medical College, Chicago, 1922. Licensed in California in 1945. Dr. Starr was a retired member of the Los Angeles County Medical Association.

TILLOTSON, MAUDE H., Sacramento. Died September 30, 1981, aged 85. Graduate of the Creighton University School of Medicine, Omaha, 1927. Licensed in California in 1929. Dr. Tillotson was a retired member of the Sacramento-El Dorado Medical Society.

New Mexico Medical Society

COHENOUR, WILLIAM E., Albuquerque. Died March 20, 1982, in Albuquerque, aged 60. Graduate of the University of Colorado School of Medicine, Denver, 1945. Licensed in New Mexico in 1947. Dr. Cohenour was a retired member of the Albuquerque and Bernalillo County Medical Association.

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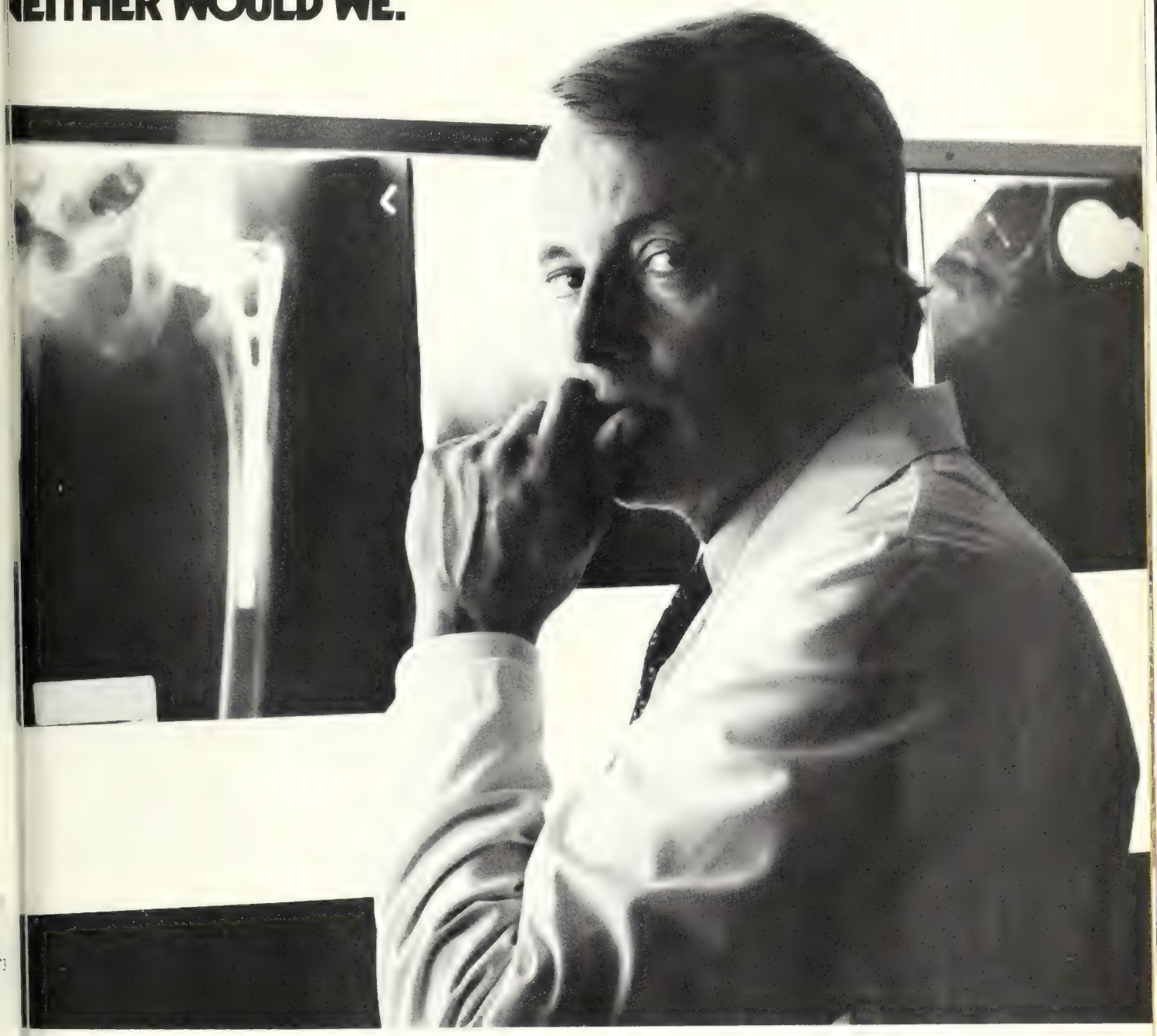

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hrs. Contact: Paul H. Jacobs, MD, Dermatology Dept., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-7813.

October 2—**TMJ: What Is It and What To Do About It.** Scripps Clinic and Research Fndn. at Hilton, San Diego. Saturday. 6 hrs. $90. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

October 2-3—**The Skin from A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Saturday-Sunday.

October 4-7—**American Academy of Family Physicians—1982 Scientific Assembly.** Moscone Center, San Francisco. Monday-Thursday. 30+ hrs. $50, members; $75, nonmembers. Contact: Edward E. Daleske, Committee on Sci. Prog., AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

October 4-7—**Practical Electrocardiography—ECG Course for Primary Physicians.** Memorial Hospital Medical Center of Long Beach at Caesar's Palace, Las Vegas. Monday-Thursday. 14 hrs. $225. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 4-9—**Review Course in Obstetrics and Gynecology and Gynecological Histopathology.** Memorial Hospital Medical Center of Long Beach at Sheraton Newport, Newport Beach. Monday-Saturday. 48 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 6-10—**American Academy for Cerebral Palsy and Developmental Medicine—36th Annual Meeting.** Sheraton Harbor Island, San Diego. Wednesday-Sunday. 26 hrs. Contact: Kevin Johns, Convention Mgr., P.O. Box 11083, Richmond, VA 23230. (804) 355-9529.

October 7-9—**CT of the Lumbar Spine.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. $275.

October 7-10—**Society of Nuclear Medicine—7th Annual Western Regional Meeting.** Town and Country, San Diego. Thursday-Sunday. Contact: Jean Parker, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

October 9—**Pediatric Ophthalmology for the Primary Care Practitioner.** Memorial Hosp. Medical Ctr.-UCI Ctr. for Health Education, Long Beach. Saturday. 6 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 9-10—**Update on Bone and Calcium.** UCSF. Saturday-Sunday.

October 9-10—**Sexual Deviation: Contemporary Psychoanalytic Views.** So. Calif. Psychoanalytic Soc. at Beverly Hilton, Beverly Hills. Saturday-Sunday. Contact: Mrs. Carol Ziff, Exec. Sec., SCPS, 9024 Olympic Blvd., Beverly Hills 90211. (213) 936-2877.

October 9-16—**Gastroenterology.** USC at Mauna Kea Beach Hotel, Kamuela. One week. 29 hrs.

October 9-17—**7th Annual International Body Imaging Conference.** West Park Hospital at Sheraton Royal Waikoloa Hotel, Kona, Hawaii. One week. 28 hrs. $385. Contact: Conf. Sec., Dept. of Radiology, West Park Hosp., 22141 Roscoe Blvd., Canoga Park 91304. (213) 340-0580, ext. 280.

October 10-15—**American Physiological Society—33rd Annual Fall Meeting.** Town and Country, San Diego. Sunday-Friday. 30 hrs. Contact: Geri Goodenough, Office of Sci. Mtgs., APS, 9650 Rockville Pike, Bethesda, MD 20814. (301) 530-7010.

October 10-15—**Annual Meeting of American Society of Plastic and Reconstructive Surgeons, Plastic Surgery Educational Foundation, and American Society of Maxillofacial Surgeons.** Sheraton Waikiki, Honolulu. Sunday-Friday. Contact: Linda Campbell, Mtg. Dept., ASPRS, 233 N. Michigan Ave., Suite 1900, Chicago 60601. (312) 856-1818.

October 10-15—**Reproductive Health Care: Changing Concepts in Fertility Regulation.** Wayne State Univ. at Marriott, Maui. Sunday-Friday. Contact: E. S. E. Hafez, Dept. of Obstetrics/Gynecology, Wayne State Univ. Sch. of Med., Med. Research Bldg., Rm. 416, 5500 E. Canfield, Detroit 48201. (313) 577-1011.

October 11-13—**6th Annual Cancer Symposium.** Scripps Memorial Hosp. at Vacation Village, San Diego. Monday-Wednesday. $300. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

October 11-14—**Hawaii Medical Association—126th Annual Scientific Meeting.** Hilton Hawaiian Village, Honolulu. Monday-Thursday. Contact: Irene Wong, Mtg. Coordinator, HMA, 320 Ward Ave., Honolulu 96814. (808) 536-7702.

October 11-15—**Emergency Medicine.** USC. Monday-Friday.

October 11-15—**Postgraduate Institute for Emergency Room Physicians—Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 33 hrs. $425.

October 11-15—**12th Annual Review Course in Gynecology and Obstetrics.** USC at Hilton, Pasadena. Monday-Friday. 35 hrs. $450.

October 13—**Post-Operative Complications—Their Prevention and Management.** LLU. Wednesday. 4 hrs.

October 14-16—**Western Society of Allergy and Immunology—21st Annual Scientific Session.** Hyatt at Union Square, San Francisco. Thursday-Saturday. Contact: Joyce M. Gullixson, Exec. Sec., 1700 S.W. Columbia, Portland 97201. (503) 224-6159.

October 15-16—**Advanced Seminar in Urologic Surgery.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

October 16—**Review Course for Gynecologic Pathology.** USC at Hilton, Pasadena. Saturday. 6 hrs. $75.

October 16-23—**4th International Seminar on Operative Arthroscopy.** UCLA at Maui. One week. 38 hrs. $785 with labs; $685, without.

October 18-25—**Pulmonary Medicine 1982: Advances and American Board Review.** USC at Hilton, Pasadena. One week.

October 20—**New Concepts in Diabetes.** Hospital of the Good Samaritan at Hilton, Los Angeles. Wednesday. 7 hrs. Contact: Bonnie VanWaardenburg, Dept. of Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

October 21-23—**California Society of Internal Medicine—Annual Meeting.** MGM Grand, Reno. Thursday-Saturday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

October 21-24—**International Symposium on the Mitral Valve.** Scripps Clinic and Research Fndn. at Hotel del Coronado, Coronado. Thursday-Sunday. 23 hrs. $350. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

October 22-24—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: Ellie Gutman, EMA, 2310 Mason St., San Francisco 94133. (415) 956-5900.

October 22-26—**American Society of Anesthesiologists.** Hilton, Las Vegas. Friday-Tuesday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

October 23-30—**Pediatrics for the Practitioner.** Memorial Hospital Medical Center of Long Beach at Mauna Kea Beach Hotel, Kamuela. One week. 20 hrs. $275. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 25-29—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 35 hrs. $350.

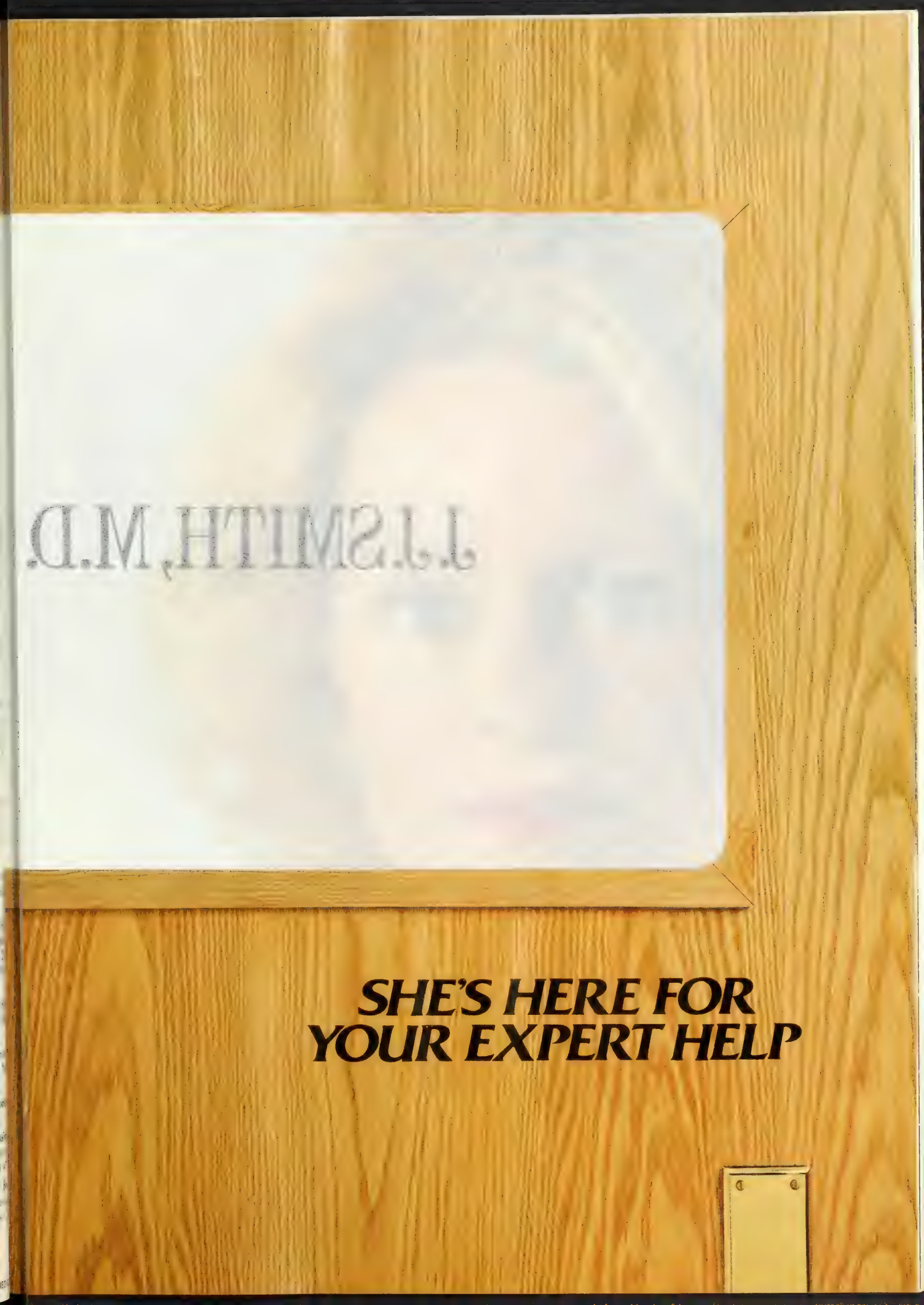
October 28-30—**Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 30—**Diagnosis and Treatment of Nasal Disorders.** UCSD. Saturday.

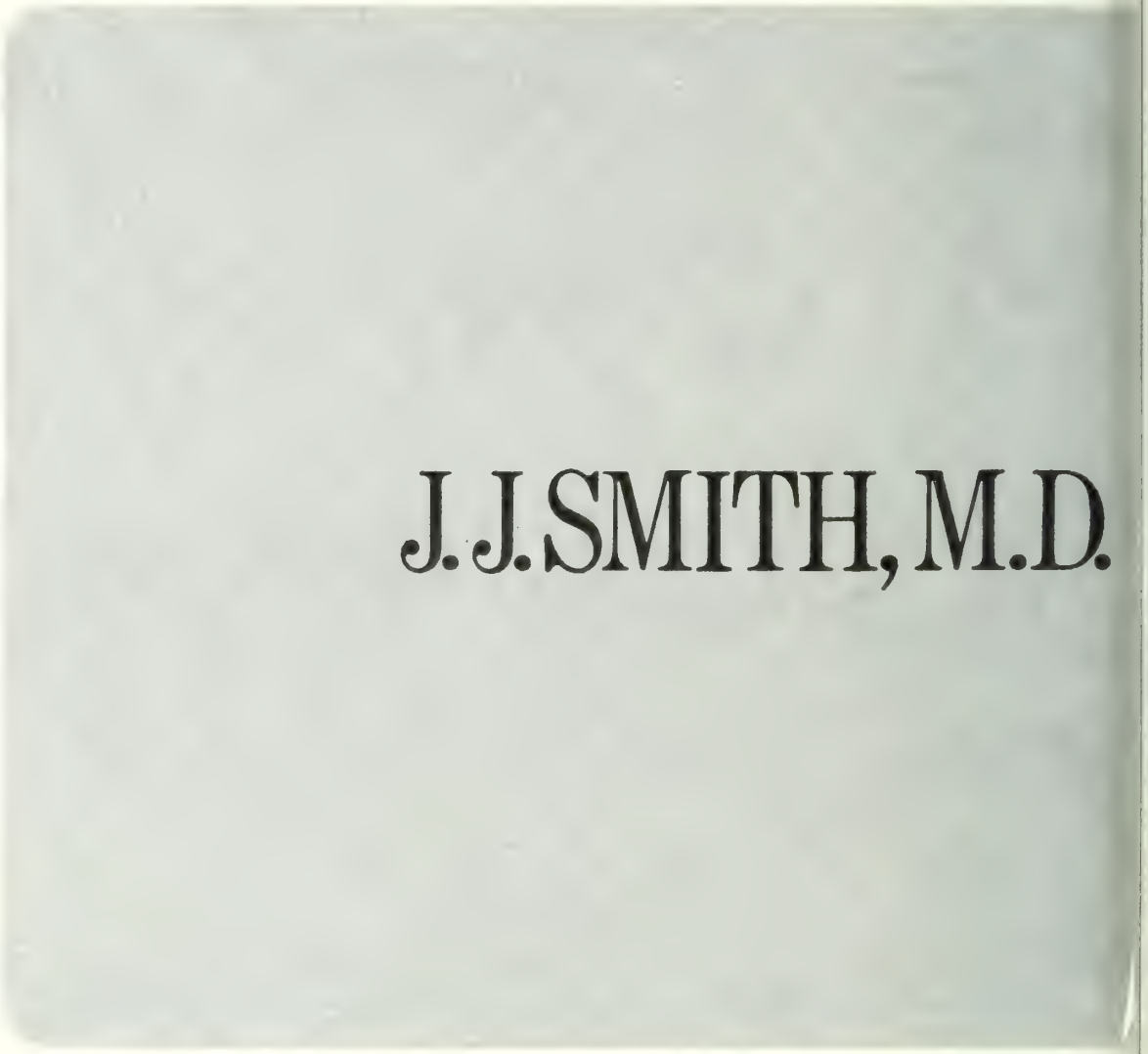
October 30-November 5—**American Academy of Ophthalmology.** Moscone Center, San Francisco. One week. Contact: AAO, P.O. Box 7424, San Francisco 94115. (415) 921-4700.

October 31-November 3—**The Practical Management of Bronchial Asthma—Symposium II.** Scripps Clinic and Research Fndn. at Rancho Bernardo. Sunday-Wednesday. 19 hrs. Con-

(Continued on Page 41)


SHE'S HERE FOR
YOUR EXPERT HELP

COUNSELING MAY HELP HER CONCERN.BU



*For moderate to severe vasomotor symptoms, atrophic vaginitis, surgical menopause, postmenopausal osteoporosis†

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

Counseling. It can help the menopausal woman through this difficult time. But counselin can't stop the moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard postmenopausal osteoporosis† the way PREMARIN tablets can.

PREMARIN. It may slow the progression of osteoporosis.† It controls her embarrassing sweats and hot flushes. Relieves her discomfor Helps her cope.** PREMARIN is a useful adjunct in your expert management of her menopausal symptoms.

PRESCRIBED WITH CAR

BUT PREMARIN® HELPS HER CONDITION*

If her menopausal symptoms are limited to atrophic vaginitis, you're aware of the rapid, virtually complete relief PREMARIN Vaginal Cream provides. In the properly selected patient, it not only relieves the distressing symptoms of estrogen deficiency, such as dyspareunia, dryness and itching, but it rebuilds vaginal tissue.

PREMARIN Vaginal Cream. You know what it can do.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms

Please see following page for Brief Summary of Prescribing Information.

for atrophic vaginitis

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM

0.625 mg/gm

BY PHYSICIANS WHO CARE.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equivalent dosage levels.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences - National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma – palliative therapy of advanced disease.
9. Postpartum breast engorgement. Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis; change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache; migraine; dizziness; mental depression; chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause: 0.3 to 1.25 mg or more daily.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism: 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure: 1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression): 1.25 mg daily, cyclically.

3. *Given for a few days.* Prevention of postpartum breast engorgement: 3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically.* Inoperable progressing prostatic cancer: 1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women: 10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

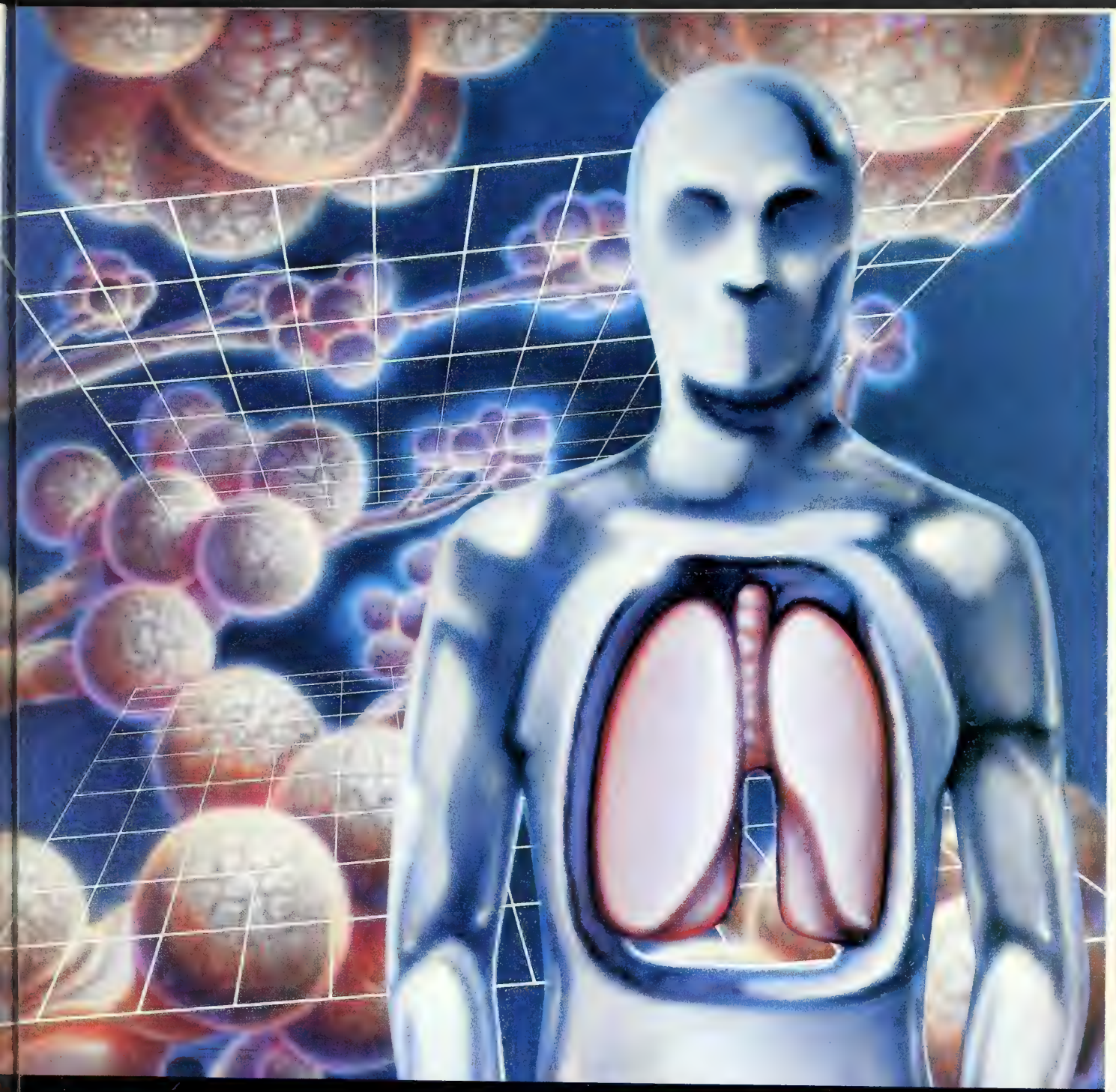
HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865 - Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866 - Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867 - Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868 - Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream - No. 872 - Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available - Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. 7814/282

Ayerst AYERST LABORATORIES
New York, N.Y. 10017



No inhaler dilates bronchioles better. Or faster. Or longer. Or more safely. Or more selectively.

That's why the aerosol bronchodilator known internationally as salbutamol* Ventolin® Inhaler is the most widely prescribed inhaler in the world.

Ventolin®
albuterol Glaxo Inhaler

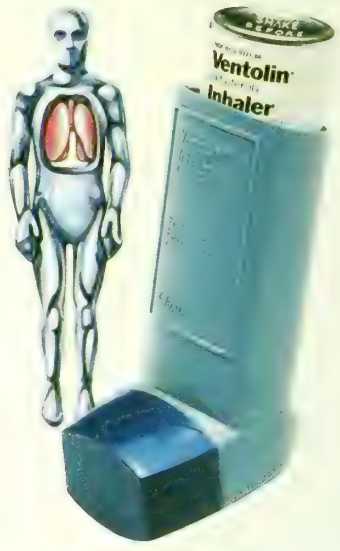
unsurpassed in the world of bronchodilation

*Official U.S. designation albuterol Ventolin® Inhaler

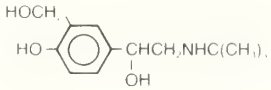
The bronchodilator with an unsurpassed clinical profile

Ventolin® albuterol Glaxo Inhaler

the most widely-prescribed inhaler in the world



DESCRIPTION The active component of VENTOLIN Inhaler is albuterol (α'-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol), a relatively selective beta$_2$-adrenergic bronchodilator having the chemical structure



Albuterol is the official generic name in the United States The international generic name for the drug is salbutamol The molecular weight of albuterol is 239 3

VENTOLIN Inhaler is a metered-dose aerosol unit for oral inhalation It contains a microcrystalline suspension of albuterol in propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid Each actuation delivers from the mouthpiece 90 mcg of albuterol Each canister provides at least 200 inhalations

CLINICAL PHARMACOLOGY The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3', 5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP) The cyclic AMP thus formed mediates the cellular responses By virtue of its relatively selective action on beta$_2$-adrenoceptors albuterol relaxes smooth muscle of the bronchi, uterus, and vascular supply to skeletal muscle, but may have less cardiac stimulant effects than does isoproterenol

Albuterol is longer acting than isoproterenol by any route of administration in most patients because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-O-methyl transferase

Because of its gradual absorption from the bronchi, systemic levels of albuterol are low after inhalation of recommended doses Studies undertaken with four subjects administered tritiated albuterol, resulted in maximum plasma concentrations occurring within two to four hours Due to the sensitivity of the assay method, the metabolic rate and half-life of elimination of albuterol in plasma could not be determined However, urinary excretion provided data indicating that albuterol has an elimination half-life of 3 8 hours Approximately 72 percent of the inhaled dose is excreted within 24 hours in the urine, and consists of 28 percent of unchanged drug and 44 percent as metabolite

Results of animal studies show that albuterol does not pass the blood-brain barrier

The effects of rising doses of albuterol and isoproterenol aerosols were studied in volunteers and asthmatic patients Results in normal volunteers indicated that albuterol is ½ to ¼ as active as isoproterenol in producing increases in heart rate In asthmatic patients similar cardiovascular differentiation between the two drugs was also seen

INDICATIONS AND USAGE VENTOLIN Inhaler is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease

In controlled clinical trials the onset of improvement in pulmonary function was within 15 minutes, as determined by both maximal midexpiratory flow rate (MMEF) and FEV_1 MMEF measurements also showed that near maximum improvement in pulmonary function generally occurs within 60 to 90 minutes following 2 inhalations of albuterol and that clinically significant improvement generally continues for 3 to 4 hours in most patients In clinical trials, some patients with asthma showed a therapeutic response (defined by maintaining FEV_1 values 15 percent or more above base line) which was still apparent at 6 hours Continued effectiveness of albuterol was demonstrated over a 13-week period in these same trials

CONTRAINDICATIONS VENTOLIN Inhaler is contraindicated in patients with a history of hypersensitivity to any of its components

WARNINGS As with other adrenergic aerosols, the potential for paradoxical bronchospasm should be kept in mind If it occurs, the preparation should be discontinued immediately and alternative therapy instituted

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs The exact cause of death is unknown, but cardiac arrest following the unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected

The contents of VENTOLIN Inhaler are under pressure Do not puncture Do not use or store near heat or open flame Exposure to temperatures above 120 F may cause bursting Never throw container into fire or incinerator Keep out of reach of children

PRECAUTIONS Although it has less effect on the cardiovascular system than isoproterenol at recommended dosages, albuterol is a sympathomimetic amine and as such should be used with caution in patients with cardiovascular disorders, including coronary insufficiency and hypertension in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes and ketoacidosis The relevance of this observation to the use of VENTOLIN Inhaler is unknown since the aerosol dose is much lower than the doses given intravenously

Although there have been no reports concerning the use of VENTOLIN Inhaler during labor and delivery, it has been reported that high doses of albuterol administered intravenously inhibit uterine contractions Although this effect is extremely unlikely as a consequence of aerosol use, it should be kept in mind

Information For Patients: The action of VENTOLIN Inhaler may last up to six hours and therefore it should not be used more frequently than recommended Do not increase the number or frequency of doses without medical consultation If symptoms get worse, medical consultation should be sought promptly While taking VENTOLIN Inhaler, other inhaled medicines should not be used unless prescribed

See Illustrated Patient Instructions For Use

Drug Interactions: Other sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol

Albuterol should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of albuterol on the vascular system may be potentiated

Beta-receptor blocking agents and albuterol inhibit the effect of each other

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In a 2 year study in the rat, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomatas of the mesovarium at doses corresponding to 111, 555, and 2,800 times the maximum human inhalational dose The relevance of these findings to humans is not known. An 18-month study in mice revealed no evidence of tumorigenicity Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility

Teratogenic Effects—Pregnancy Category C: Albuterol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human dose There are no adequate and well-controlled studies in pregnant women Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus A reproduction study in CD-1 mice with albuterol (0 025, 0 25, and 2 5 mg/kg, corresponding to 1 4, 14, and 140 times the maximum human inhalational dose) showed a cleft palate formation in 5 of 111 (4.5 percent) fetuses at 0 25 mg/kg and in 10 of 108 (9 3 percent) fetuses at 2 5 mg/kg None were observed at 0 025 mg/kg Cleft palate also occurred in 22 of 72 (30 5 percent) fetuses treated with 2.5 mg/kg isoproterenol (positive control) A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37 percent) fetuses at 50 mg/kg, corresponding to 2,800 times the maximum human inhalational dose

Nursing Mothers: It is not known whether this drug is excreted in human milk Because of the potential for tumorigenicity shown for albuterol in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established

ADVERSE REACTIONS The adverse reactions of albuterol are similar in nature to those of other sympathomimetic agents, although the incidence of certain cardiovascular effects is less with albuterol A 13-week double-blind study compared albuterol and isoproterenol aerosols in 147 asthmatic patients The results of this study showed that the incidence of cardiovascular effects was palpitations, less than 10 per 100 with albuterol and less than 15 per 100 with isoproterenol The incidences of tachycardia and increased blood pressure were 10 per 100 and less than 5 per 100, respectively, with both drugs In the same study, both drugs caused tremor or nausea in less than 15 patients per 100, dizziness or heartburn in less than 5 per 100 patients Nervousness occurred in less than 10 per 100 patients receiving albuterol and in less than 15 per 100 patients receiving isoproterenol

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vomiting, vertigo, central stimulation, insomnia, headache, unusual taste, and drying or irritation of the oropharynx

OVERDOSAGE Exaggeration of the effects listed in ADVERSE REACTIONS can occur Anginal pain and hypertension may result

The oral LD_{50} in male and female rats and mice was greater than 2,000 mg/kg. The aerosol LD_{50} could not be determined

Dialysis is not appropriate treatment for overdosage of VENTOLIN Inhaler The judicious use of a cardioselective beta-receptor blocker, such as metoprolol tartrate, is suggested, bearing in mind the danger of inducing an asthmatic attack

DOSAGE AND ADMINISTRATION The usual dosage for adults and children 12 years and older is 2 inhalations repeated every 4 to 6 hours, in some patients, 1 inhalation every 4 hours may be sufficient More frequent administration or a larger number of inhalations is not recommended The use of VENTOLIN Inhaler can be continued as medically indicated to control recurring bouts of bronchospasm During this time most patients gain optimal benefit from regular use of the inhaler Safe usage for periods extending over several years has been documented

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma which would require reassessment of therapy

HOW SUPPLIED VENTOLIN Inhaler, 17 0 g canister, box of one Each actuation delivers 90 mcg of albuterol from the mouthpiece It is supplied with an oral adapter and patient's instructions. (NDC-0173-0321-88)

Store between 15° and 30° C (59° to 86° F).

Glaxo

Manufactured by Glaxo Operations UK, Ltd.,
Greenford, England
For Glaxo Inc.,
Fort Lauderdale, Florida 33309

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OCTOBER-1981

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(Continued from Page 36)

tact: Dianne Tisue, Dept. of Academic Affairs, 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

November 1-3—**Practical Management of Bronchial Asthma—Symposium II.** Scripps Clinic and Research Fndn. at Rancho Bernardo Inn, San Diego. Monday-Wednesday. 19 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037.

November 1-4—**Interstate Postgraduate Medical Association—Scientific Assembly.** Town and Country, San Diego. Monday-Thursday. 24 hrs. Contact: H. B. Maroney, Exec. Dir., IPMA, P.O. Box 1109, Madison, WI 53701. (608) 257-6781.

November 1-5—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $365.

November 4-6—**Sterling Bunnell Memorial Lectureship.** UCSF (Dept. of Orth. Surg.). Thursday-Saturday.

November 7-12—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui. Sunday-Friday. $350.

November 7-13—**Allergy and Immune Diseases.** Symposium Maui, Inc., and Hawaii Chap., AAFP, at Lahaina Resort, Kaanapali, Maui. One week. 22 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., P.O. Box 10185, Lahaina, Maui, HI 96761.

November 10—**Pediatric Emergencies.** LLU. Wednesday. 4 hrs.

November 11-14—**Allergy/Immunology: Practical Aspects Today and Into the 21st Century.** American Assn. for Clinical Immunology and Allergy at Marriott, Anaheim. Thursday-Sunday. 30 hrs. $250. Contact: Howard S. Silber, Exec. Dir., AACIA, P.O. Box 912-DTS Omaha NE 68101. (402) 551-0801.

November 14-17—**California Academy of Family Physicians—Annual Meeting.** Hotel del Coronado Coronado. Sunday-Wednesday. Contact: CAFP, Suite 820, The Hearst Bldg., 5 Third St., San Francisco 94103. (415) 541-0762.

November 18-21—**Modern Concepts in Operative Neurosurgery, Critical Care and Rehabilitation.** Comprehensive Central Nervous System Injury Fndn. and Institute for Medical Education and Research at Hilton on Mission Bay, San Diego. Friday-Sunday. 20 hrs. $250. Contact: CNS Injury Fndn., P.O. Box 9494, San Diego 92109. (714) 272-3126.

November 19-22—**Pediatric Update.** Calif. Chapters, American Academy of Pediatrics, at Hilton, Las Vegas. Friday-Monday. 14 hrs. $195, members; $220, nonmembers. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

November 28-December 10—**Temporal Bone Surgical Dissection Course.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, House Ear Inst., 256 S. Lake St., Los Angeles 90057.

December 2-4—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. 23 hrs. Contact: Luis M. de la Maza, MD, PhD, Dept. of Pathology, UCI Med. Ctr., Orange 92668. (714) 634-6868.

December 3-5—**Perioperative Cardiac Dysfunction.** Cardiothoracic Research and Education Fndn. at Hilton Beach Resort, San Diego. Friday-Sunday. 16 hrs. $250. Contact: CREF, P.O. Box 33185, San Diego 92103. (714) 272-3126.

December 4—**Photocoagulation Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $250. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Ed., Los Angeles 90024. (213) 825-4617.

December 5-7—**Leucocyte Conference.** USC at Asilomar, Pacific Grove. Sunday-Tuesday.

December 8—**Chronic Diarrhea—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs.

December 9-12—**American Academy of Psychoanalysis—26th Winter Meeting.** Hotel del Coronado, Coronado. Thursday-Sunday. 20 hrs. Contact: Vivian Mendelsohn, Admin. Dir., AAP, 30 E. 40th St., Suite 608, New York 10016. (212) 679-4105.

December 13-17—**Postgraduate Institute for Emergency Room Physicians—Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 33 hrs. $425.

ALASKA

See Washington Listings: June 17-18.

IDAHO

July 28-31—**Idaho Medical Association 90th Annual Meeting.** Sun Valley. For information contact IMA, P.O. Box 2668, Boise, ID 83761. (208) 344-7888.

See also Utah Listings: August 2-6.

See also Washington Listings: February 14-17.

MONTANA

September 9-11—**Adult and Pediatric Chest Diseases—Current Views 1982.** Bigfork. Thursday-Saturday. Flathead Lake Lodge. Contact: American Lung Association of Montana, 828 Helena Ave, Helena, MT 59601. (406) 442-6556.

September 30-October 2—**Montana Medical Association Annual Meeting.** Great Falls. Thursday-Saturday. Sheraton. For information contact: Montana Medical Association, 2011 Eleventh Avenue, Suite 12, Helena, MT 59601. (406) 443-4000.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

June 17-19—**Radiology for Primary Care Physicians 1982—An Update.** Santa Fe. Thursday-Saturday. Symposia de Santa Fe. 15 credit hours, also AAFP Prescribed. Contact: Marcus J. Smith, MD, PO Box 5175, Santa Fe, NM 87501. (505) 982-5218.

July 8-10—**25th Annual Meeting, New Mexico Ophthalmological Society.** Santa Fe. Thursday-Saturday. Hilton Inn. 8 credit hours. Contact: Walter J. Levy, MD, 465 St. Michael's Dr., Santa Fe, NM 87501. (505) 982-1911.

July 19-22—**25th Annual Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 credit hours. Also AAFP Prescribed. Contact: Convention Director, NM Academy of Family Physicians, PO Box 456, Sunland Park, NM 88063. (505) 266-7868 or (915) 533-3449.

July 23-25—**11th Annual Santa Fe Cardiology Symposium.** Santa Fe. Friday-Sunday. Inn at Loretto. 14 credit hours, also AAFP Prescribed. Contact: Meeting Director, Southwest Cardiology Associates, 8100 Constitution NE, Albuquerque, NM 87110. (505) 292-1114.

July 29-31—**General Surgical Update—82.** Albuquerque. Thursday-Saturday. Classic Hotel. 15 credit hours, also AAFP

(Continued on Page 52)

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(Continued on Page 44)

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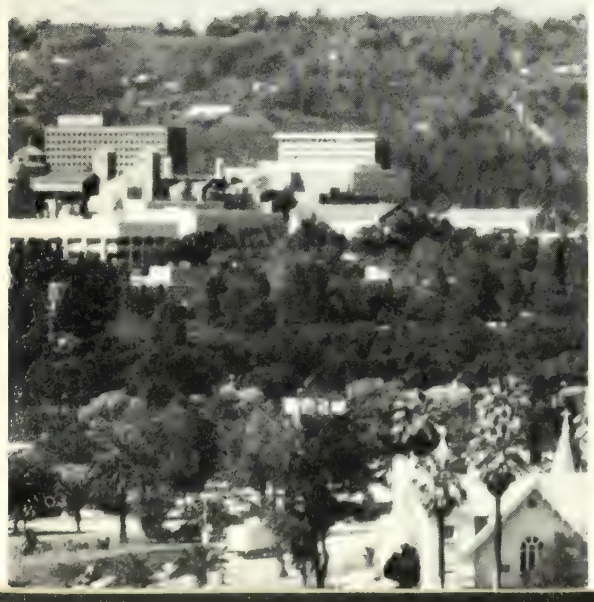

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RIMSO®-50
(dimethyl sulfoxide)
50% w/w aqueous solution

INDICATIONS AND USAGE

RIMSO® - 50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis RIMSO ® - 50 has not been approved as being safe and effective for any other indication There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract

CONTRAINDICATIONS

None known

WARNINGS

Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide This hypersensitivity has been reported in one patient receiving intravesical RIMSO® - 50 The physican should be cognizant of this possibility in prescribing RIMSO® - 50 If anaphylactoid symptoms develop, appropriate therapy should be instituted

PRECAUTIONS

Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations are recommended prior to and periodically during treatment Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count

Intravesical instillation of RIMSO® - 50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation

Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications

Pregnancy Category C Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (2 5-12 gm/kg) Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2 5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1 1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities There are no adequate and well controlled studies in pregnant women Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman

Safety and effectiveness in children have not been established

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO® - 50 (dimethyl sulfoxide) This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide

The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration

DOSAGE AND ADMINISTRATION

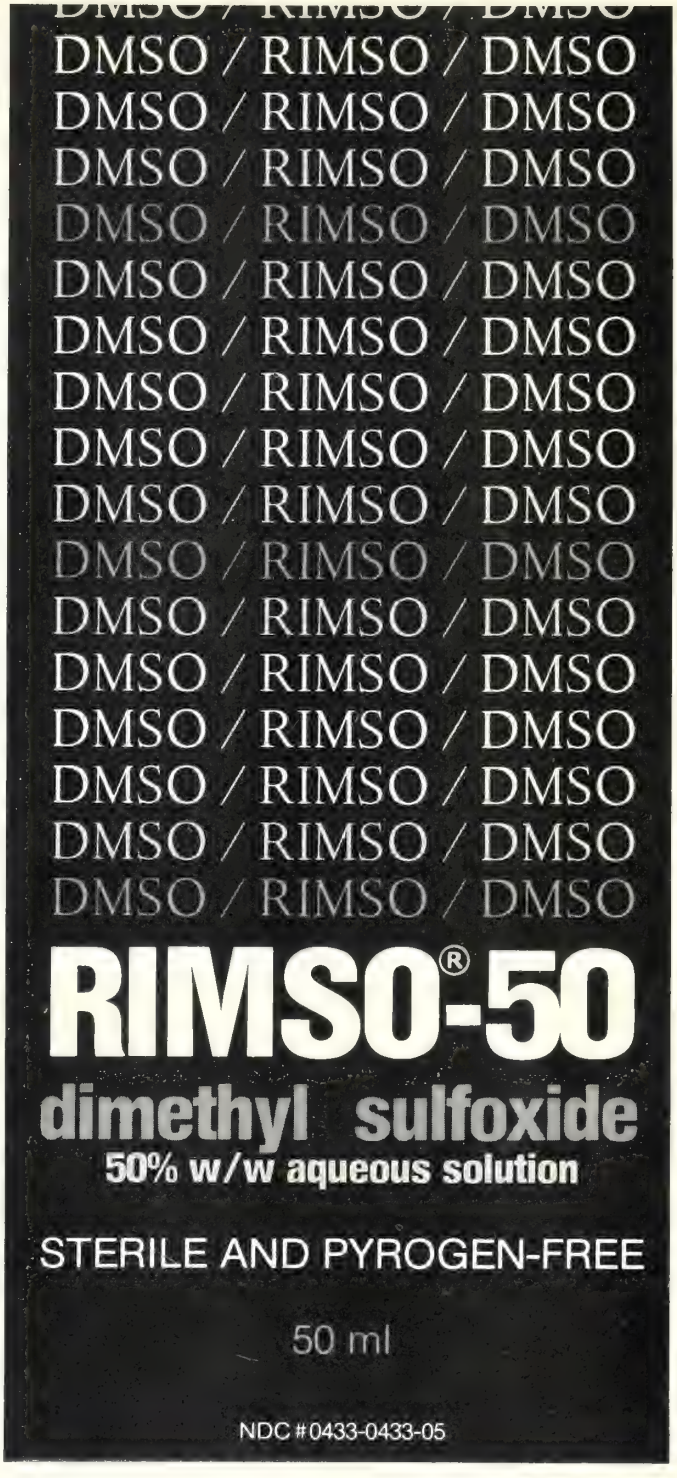
Instillation of 50 ml of RIMSO® - 50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes Application of an analgesic lubricant gel such as lidocaine jelly to the uretha is suggested prior to insertion of the catheter to avoid spasm The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained Thereafter, time intervals between therapy may be increased appropriately

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO® - 50 can reduce bladder spasm

In patients with severe interstital cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia (Saddle block has been suggested)

HOW SUPPLIED

Bottles contain 50 ml of sterile and pyrogen-free RIMSO® - 50 (50% w/w dimethyl sulfoxide aqueous solution)
Dimethyl sulfoxide is clear and colorless
Protect from strong light
Store at room temperature (50° to 86°F) (15° to 30°C)
Do not autoclave
NDC # 0433-0433-05



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(Continued from Page 42)

PHYSICIANS WANTED

FAMILY PRACTITIONER to join established group in small central California community. Interest in OB desired. Excellent hospital facilities available. Partnership available. Contact Dr. L. Kahler, Tracy Medical Group, 500 E. 11th Street, Tracy, CA 95376. (209) 835-4232.

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(Continued on Page 46)

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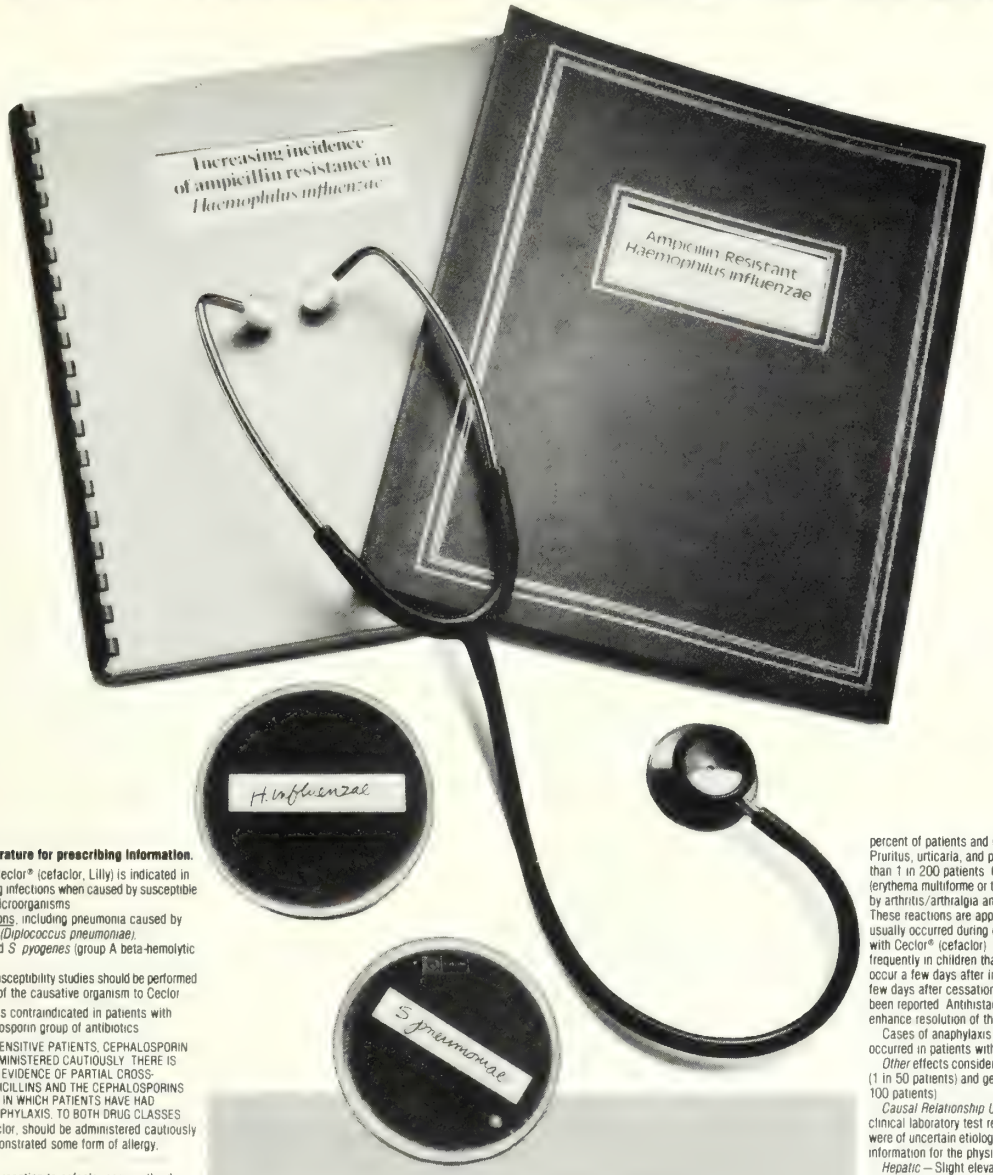
An added complication... in the treatment of bacterial bronchitis*


Increasing incidence of ampicillin resistance in Haemophilus influenzae
Ampicillin Resistant Haemophilus influenzae
H. influenzae
S. pneumoniae

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor
Pulvules®, 250 and 500 mg

Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* and *S pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e g , pressor amines, antihistamines or corticosteroids

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coomb testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below

Gastrointestinal symptoms occur in about 2 5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90)

As with other broad-spectrum antibiotics, colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with Ceclor

Hypersensitivity reactions have been reported in about 1 5 percent of patients and include morbilliform eruptions (1 in 100) Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor® (cefaclor) Such reactions have been reported more frequently in children than in adults Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy No serious sequelae have been reported Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [100281R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S pneumoniae* or *H influenzae*.[8]

Note Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever See prescribing information

References

1 Antimicrob Agents Chemother , *8*:91, 1975
2 Antimicrob Agents Chemother , *11*:470, 1977
3 Antimicrob Agents Chemother , *13*:584, 1978
4 Antimicrob Agents Chemother , *12*:490, 1977
5 Current Chemotherapy (edited by W Siegenthaler and R Luthy), II 880 Washington, D C American Society for Microbiology, 1978
6 Antimicrob Agents Chemother , *13*:861, 1978
7 Data on file, Eli Lilly and Company
8 Principles and Practice of Infectious Diseases (edited by G L Mandell, R G Douglas, Jr , and J E Bennett), p 487 New York John Wiley & Sons, 1979

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

200066

(Continued from Page 44)

PHYSICIANS WANTED

ASSISTANT PROFESSOR IN RESIDENCE, NEPHROLOGY AND METABOLISM, DEPARTMENT OF MEDICINE, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO. Junior faculty position to pursue studies in the metabolic basis of disorders of the renal tubule. Applicants should have a thorough understanding of renal metabolism, particularly in the area of metabolic generation of energy and its relationship to transepithelial transport. Applicants should also have a demonstrated ability to do experimental work in the area of induced disorders of renal metabolism that in turn induce disorders in transepithelial transport. It would be helpful if applicants have experience in investigating disordered adenine nucleotide metabolism in animal models of disordered functions of the rental tubule. Applicants must be board certified in internal medicine and nephrology and be a United States citizen. Please send curriculum vitae promptly to: R. Curtis Morris, Jr., MD, Director, General Clinical Research Center, 1202 Moffitt Hospital, University of California, San Francisco, San Francisco, CA 94143. UCSF is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.

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SEEK POSITION IN PRIMARY CARE—Group, Clinic, Hospital. Board Eligible internist. Reply to Box 6280. The Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

ER PHYSICIAN. Seeks directorship or ER contract. Six years experience, including scheduling, management, audits, quality assurance, education. ACLS, ATLS. Write Box 6302, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

WOMAN PHYSICIAN. Board certified in internal medicine interested in seeking an associate in the San Francisco area (prefer making use of my Spanish language) or working with an institution as a consultant. Available now. Reply: Margarita Martinez, MD, 888 44th Ave, San Francisco, CA 94121.

PRACTICES AVAILABLE

PRACTICE and EQUIPMENT. Ophthalmologist retiring. Will sell practice and/or equipment for cost of equipment only. Phone or write to: Joseph S. Holowin, MD, 710 S. Brookhurst, Suite A, Anaheim, CA 92804. (714) 772-5740.

TO SELL OR BUY A MEDICAL PRACTICE, or to arrange an association, contact Physicians Clearinghouse, Mary Bradshaw, 21 Altamount Dr., Orinda, CA 94563. (415) 376-0762. Consulting, Appraising, Partnerships, Placement.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANNUAL REVIEW OF NEUROSCIENCE—Volume 5, 1982—Editor: W. Maxwell Cowan; Associate Editors: Zach W. Hall and Eric R. Kandel. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, CA 94306, 1982. 392 pages, $22.00 (USA), $25.00 (elsewhere).

THE ELBOW—Edited by Thomas G. Wadsworth, MChOrth, FRCS, FRCSE, FACS, FICS; Foreword by S. Benjamin Fowler, MD. Churchill Livingstone Inc., 19 West 44th Street, New York, NY 10036, 1982. 354 pages, $50.00.

CARDIAC SURGERY IN PATIENTS WITH CHRONIC RENAL DISEASE—Edited by Jack Love, DPhil, MD. Futura Publishing Company, 295 Main Street, Mount Kisco, NY 10549, 1982. 194 pages, $26.00.

CLINICAL DISORDERS OF THE SHOULDER—Lipmann Kessell, MBE(Mlty), MC, FRCS. Churchill Livingstone Inc., 19 West 44th Street, New York, NY 10036, 1982. 182 pages, $50.00.

COPING IN MEDICAL SCHOOL—Bernard Virshup, MD. Health Sciences Consortium, Inc., 200 Eastowne Drive, Suite 213, Chapel Hill, NC 27514, 1981. 130 pages, $9.95 (paperback).

CURRENT PEDIATRIC DIAGNOSIS & TREATMENT—Seventh Edition—C. Henry Kempe, MD; Henry K. Silver, MD; Donough O'Brien, MD, FRCP, and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1982. 1,106 pages, $26.00.

EPILEPSY AND PSYCHIATRY—Edited by E. H. Reynolds, MD, FRCP, and M. R. Trimble, MB, BSc, MPhil, MRCP, MRCPsych. Churchill Livingstone Inc., 19 West 44th Street, New York, NY 10036, 1981. 379 pages, $55.00.

14 DAYS TO A WELLNESS LIFESTYLE—Donald B. Ardell, PhD. Whatever Publishing, Inc., 158 E. Blithedale, Mill Valley, CA 94941, 1982. 378 pages, $8.95 (paperback).

MacKEITH'S INFANT FEEDING AND FEEDING DIFFICULTIES—Sixth Edition—Christopher B. S. Wood, MB, FRCP, DCH, and John A. Walker-Smith, MD, FRCP, FACP, Churchill Livingstone Inc., 19 West 44th Street, New York, NY 10036, 1981. 334 pages, $20.00 (paperback).

NATIONAL PARENTS' MOVEMENT FOR DRUG FREE YOUTH—Pride Southeast Drug Conference Proceedings, 1980 and 1981—Editors: Thomas J. Gleaton, EdD; Keith Manatt Schuchard, PhD, and Helen W. Moore. Parents' Resource Institute for Drug Education, Inc., 930 Crestline Road, NE, Atlanta, GA 30328, 1982. 206 pages, no price given (paperback).

PAEDIATRIC CARDIOLOGY—Volume 4: Proceedings of the World Congress of Paediatric Cardiology held in London in 1980—Edited by M. J. Godman, MB, ChB(Ed), FRCP(Ed); Foreword by Fergus J. Macartney, MB, BChir, FRCP, and Jane Somerville, MD, MB, BS, FRCP. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1981. 788 pages, $79.00.

PHYSICIANS' GUIDE TO DISEASES OF THE ORAL CAVITY—Harriet S. Goldman, DDS, MPH, and Michael Z. Marder, DDS. Medical Economics Books, (DPRKI), Box 157, Florence, KY 41042, 1982. 230 pages, *$39.50 plus $1.25 handling charge. *Prices are subject to change.

PHYSICIAN'S HANDBOOK—Twentieth Edition—Marcus A. Krupp, MD; Lawrence M. Tierney, Jr, MD; Ernest Jawetz, MD, PhD; Robert L. Roe, MD, and Carlos A. Camargo, MD. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1982. 774 pages, $12.00.

PHYSIOLOGY OF THE KIDNEY—Second Edition—Lawrence P. Sullivan, PhD, and Jared J. Grantham, MD. Lea & Febiger, 600 Washington Square, Philadelphia, PA 19106, 1982. 236 pages, illustrated, $14.50 (Canada $17.50) (paperback).

RECENT ADVANCES IN CLINICAL NEUROLOGY—Number Three—Edited by W. B. Matthews, DM, FRCP, and Gilbert H. Glaser, MD, MedScD. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1982. 254 pages, $27.50 (softbound).

RECENT ADVANCES IN GERIATRIC MEDICINE—Edited by Bernard Isaacs, MD, FRCP (Glas), MRCP (Edin). Churchill Livingstone Inc., 19 West 44th Street, New York, NY 10036, 1978. 172 pages, $25.00.

RECENT ADVANCES IN HAEMATOLOGY—Third Edition—Edited by A. V. Hoffbrand, MA(Oxon), DM, FRCP(Lond), RRCPath. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1982. 352 pages, $40.00 (paperback).

RECENT ADVANCES IN OCCUPATIONAL HEALTH—Edited by J. C. McDonald, MD, FRCP, FFCM, FFOM. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1981. 292 pages, $40.00 (softbound).

ULTRASTRUCTURAL APPEARANCES OF TUMOURS—A Diagnostic Atlas—Douglas W. Henderson, MB, BS, FRCPA, and John M. Papadimitriou, MD, PhD, MRCPath, FRCPA; Foreword by Richard L. Kempson, MD. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1982. 409 pages, illustrated, $89.00.

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FRIDAY, AUGUST 13

8:00 Registration

8:30 GEORGE E. OMER, MD
Evaluation of Injuries of the Hand

9:15 JAMES L. CHRISTENSEN, MD
Sports Injuries to the Elbow and Forearm

10:30 GEORGE E. OMER, MD
Sports Injuries to the Wrist

11:15 OMER, DALES, CHRISTENSEN
Panel—Discussion of Hand, Elbow, Wrist

noon Luncheon—SACHIKO ST. JEOR, PhD
Nutrition and Running

1:30 CLARENCE SHIELDS, MD
LA Rams Team Physician
Rotator Cuff Injuries: Diagnosis and Treatment

2:15 JERRY MAY, PhD
Physical Injuries of the Elite Athlete

SATURDAY, AUGUST 14

8:30 CLARENCE SHIELDS, MD
Muscle Physiology and Rehabilitation

9:15 JOHN PEACOCK, MD
Sports Injuries to the Neck

10:00 GEORGE E. OMER, MD
Compression Syndromes of Elbow, Wrist an Fingers

11:00 STEPHEN DOW, MD
Running Injuries

11:30 RANDY JACOBY, RPT
Fitness Evaluation Update, 1982

noon Lunch on your own

1:30 E. JAMES GREENWALD, MD
Football Injuries

2:00 RICHARD STEADMAN, MD
Olympic Ski Team Physician
Skiing Injuries

2:30 STEADMAN, JACOBY, DOW, GREENWALD
Panel—Sports Injuries

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USC

THE TWELFTH ANNUAL REVIEW COURSE IN GYNECOLOGY AND OBSTETRICS

This comprehensive course will be held at the Pasadena Hilton Hotel, Pasadena, California, Monday through Friday, October 11-15, 1982. It will review many basic concepts and update clinical management in every area of obstetrics and gynecology. Although the program will appeal to all, its direction will be toward those preparing for recertification examinations or the Oral OB/GYN Boards. A complete, well-organized syllabus covering the entire five-day program will be supplied each participant.

TUITION: $450 (includes 5 lunches)
CREDIT: 35 hours

Immediately following is the **REVIEW COURSE FOR GYNECOLOGIC PATHOLOGY,** scheduled for Saturday, October 16, 1982, also at the Pasadena Hilton. Review of pathological changes which occur in the female genital tract in response to inflammatory, neoplastic and abnormal hormonal stimuli as well as concepts of diagnosis and pathogenesis will be discussed; current terminology used in diagnosis will be emphasized. This course is designed primarily to assist those physicians who are preparing for the American Board of Obstetrics and Gynecology examinations.

TUITION: $75 (includes lunch)
CREDIT: 6 hours

PERINATAL MEDICINE

This comprehensive course will be held at the Royal Lahaina in Maui, Hawaii, February 5-11, 1983. The course will focus on current management approaches to solve clinical problems. The "Case Management Problems" will begin with the presentation of a difficult clinical case. Question and answer sessions will be emphasized.

TUITION: $425
CREDIT: 23 hours

Contact: **Associate Dean, USC School of Medicine, Postgraduate Div., 2025 Zonal Ave., Los Angeles, CA 90033; (213) 224-7051.**

(Continued from Page 41)

Prescribed. Contact: UNM School of Medicine, Office of CME, Albuquerque, NM 87131. (505) 277-3942.

August 27-28—**Pediatric-Adolescent Sports Medicine.** Albuquerque. Friday-Saturday. Hilton Inn. 9 credit hours, also AAFP Prescribed. Contact: Tom Bodnar, Albuquerque & Bernalillo County Medical Association, 303 San Mateo NE, Suite 203, Albuquerque, NM 87108. (505) 268-2446.

October 7-9—**The Clinical Spectrum of Adult Heart Disease.** Albuquerque. Thursday-Saturday. University of New Mexico School of Medicine Auditorium. Hour for hour credit, also AAFP Prescribed. Contact: Jonathan Abrams, MD, UNM, School of Medicine, Dept. of Cardiology, Albuquerque, NM 87131. (505) 277-4253.

October 14-16—**The 12-Lead ECG for the Primary Care Physician.** Albuquerque. Thursday-Saturday. Presbyterian Hospital. 23 credit hours, also AAFP Prescribed. Contact: NM Heart Institute, 2403 San Mateo NE, Albuquerque, NM 87108. (505) 884-3717.

November 12-13—**New Mexico Medical Society Interim Meeting.** Las Vegas, New Mexico. Friday-Saturday. Highlands University. 7 credit hours, also AAFP Prescribed. Contact: NM Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

January 15-16—**Semi-Annual Clinical Meeting: New Mexico Academy of Family Physicians.** Albuquerque. Saturday-Sunday. Marriott Hotel. 12 credit hours, also AAFP Prescribed. Contact: New Mexico Academy of Family Physicians, 303 San Mateo NE, #204, Albuquerque, NM 87108. (505) 266-7868.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

OBSTETRICS AND GYNECOLOGY

October 21-23—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

SURGERY

December 3—**Soft Tissue Surgery Techniques.** Portland. Friday. Oregon Health Sciences University Campus. For information contact: OHSU-CME.

INTEREST TO ALL PHYSICIANS

June 18—**Small Cell Carcinoma of the Lung.** Portland. Friday. Oregon Medical Association Building. For information contact: OHSU-CME.

June 24-25—**Urology for the Non-Urologist.** Portland. Thursday-Friday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

September 10-11—**Ashland Conference: Antimicrobial Therapy in Perspective: The Place of the New Drugs.** Ashland. Friday-Saturday. Ashland Hills Inn. For information contact: OHSU-CME.

October 29-31—**Salishan Conference: Cardiology.** Gleneden Beach. Friday-Saturday. Salishan Lodge. For information contact: OHSU-CME.

November 4-5—**Sommer Lectures—Oregon Medical Association Annual Meeting.** Portland. Thursday-Friday. Thunderbird Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

November 18-19—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

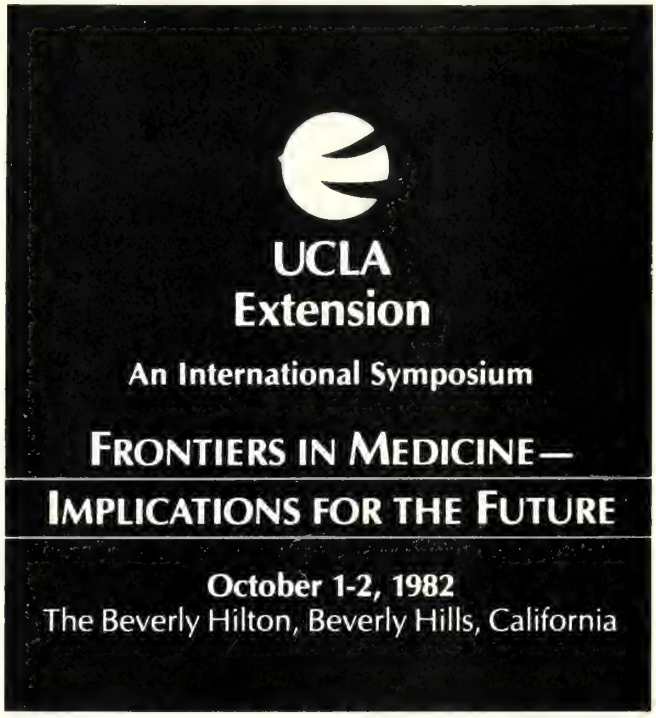
UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:



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- **Will recent advances in knowledge of the aging process enable us to slow or reverse it within the next decade?**

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For brochure and complete information, contact UCLA Extension, Continuing Education in Health Sciences/WJ, 10995 Le Conte Avenue, Los Angeles, CA 90024, (213) 825-8421.

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

MKSAP V REVIEW

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University Medical Center, Salt Lake City

October 1981-June 1982 (Ongoing)—Thursdays. 2 hrs. Fee for Optional Materials: $160 (ACP non-members); $60 (ACP members). Contact: John Holbrook, MD (801) 581-7818.

* * * *

June 21-24—**Alcoholism and Other Drug Dependencies** (Sponsor: University of Utah). Salt Lake City. Monday-Thursday. Browning Lecture Hall, University of Utah Campus. 25 hrs. Fee: $250. Contact: James R. Swenson, MD (801) 581-7985.

June 22-24—**Training and Certification of Pulmonary Function Testing.** (Sponsor: University of Utah). Park City. Tuesday-Thursday. 17.5 hrs. Fee: $350. Contact: Katharine Blosch (801) 581-5710.

June 23-25—**5th Annual Cardiovascular Conference** (Sponsors: Utah Heart Association/Bureau of Chronic Disease, Utah State Health Department). Salt Lake City. Wednesday-Friday. 15 hrs. Fee: $35. Contact: Kathy Kogianes (801) 533-6141.

June 28-29—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Monday-Tuesday. Hilton Inn. 14.5 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

July 21-25—**Current Concepts in Digital Subtraction Angiography, CT of Spine, CT of Temporal Lobe, CT of Pharynx, Larynx, Neck** (Sponsor: University of Utah). Wednesday-Sunday. Jackson Hole, Wyoming. Fee: To be announced. Credit: To be announced. Contact: F. Matsuo, MD (801) 581-8188.

August 2-6—**Pediatric Immunology and Infectious Diseases** (Sponsor: University of Utah). Sun Valley Lodge, Idaho. Fee: To be announced. 25 hrs. Contact: Harry Hill, MD, John Matsen, MD (801) 581-5514.

August 5-6—**Utah Perinatal Association Annual Meeting** (Sponsor: University of Utah). Park City. Monday-Friday. 12 hrs. Fee: $70. Contact: Nan Streeter, RN (801) 277-8458.

September 15-17—**Annual Utah State Medical Association Meeting** (Sponsors: University of Utah/Utah State Medical Association). Salt Lake City. Wednesday-Friday. Hotel Utah. Fee: To be announced. Credit: To be announced. Contact: Maxcine Fry (801) 355-7477.

September 17—**Pediatric Ophthalmology Meeting: Eye Problems of Children** (Sponsor: University of Utah). Snowbird. Friday. 6 hrs. Fee: $15-$35. Contact: Jane Kivlin, MD (801) 581-6384.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

June 15—**Vaginitis.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

June 15—**Site Visit.** Spokane. Tuesday. Sacred Heart Medical Center. Contact: U/W.

June 16—**Site Visit.** Anacortes. Wednesday. Contact: U/W.

June 17-18—**(ALASKA) Behavior Medicine for GP's.** Anchorage. Thursday-Friday. Contact: U/W.

June 19-23—**(BRITISH COLUMBIA, CANADA) Canadian Congress of Laboratory Medicine & Pacific Northwest Society of Pathologists Meeting.** Vancouver, BC. Saturday-Wednesday. Hotel Vancouver. Contact: G. R. Gray, MD, 201-660 West Seventh Avenue, Vancouver, BC V5Z IB5.

June 22—**Pearls in Office Practice—6th Annual Family Practice Day.** Seattle. Tuesday. Group Health Central Campus. Contact: Marilyn Russell, 201 16th Ave., East, Seattle, WA 98112. (206) 326-7349.

June 23-27—**(OREGON) Modern Medical Practice.** Ashland. Wednesday-Sunday. Ashland Inn. Contact: U/W.

June 24-25—**EKG Interpretation and Arrythmias.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

June 24-26—**Scientific Aspects of Dance.** Seattle. Thursday-Saturday. Seattle Central Community College. Contact: U/W.

June 28—**Recent Advances in Hematology.** Wenatchee. Monday. Central Washington Hospital. Contact: U/W.

July 15-16—**Surviving the Elements.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

July 23—**Marriage of the Professional.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

July 23-25—**Washington State Society of Anesthesiologists: Seafair IV Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center. Contact: VMMC.

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COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

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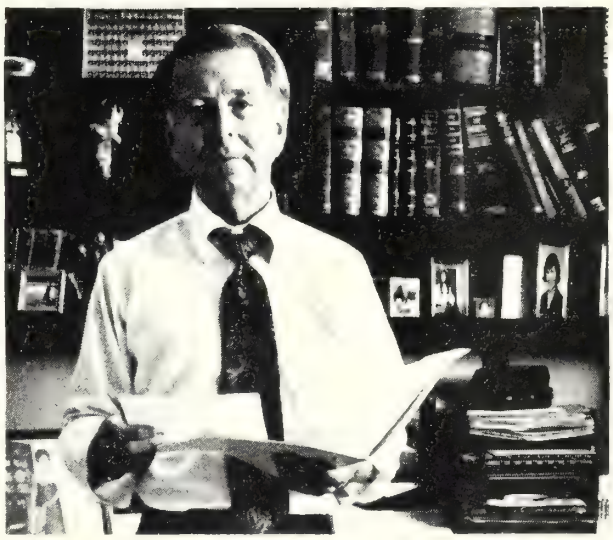
Contact your local Arthritis Foundation chapter for the latest information on arthritis. This includes continuing educational seminars by leading rheumatologists, scientific meetings, "outreach" programs—as well as the "Bulletin on the Rheumatic Diseases," "Arthritis and Rheumatism Journal," "Primer on the Rheumatic Diseases," audio cassettes and other professional materials. Free disease handbooks and medication pamphlets are also available to patients.

Please. Let us help your practice with what we teach.

The Arthritis Foundation helps doctors help.



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WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: June 6-8, 1982, Chena Hot Springs.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: 1983—date and place to be announced.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 11-16, 1983, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 21-24, 1982, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 11-14, 1982, Hilton Hawaiian Village, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 28-31, 1982, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: September 30-October 2, 1982, Sheraton, Great Falls.

Nevada State Medical Association—3660 Baker Lane. Reno 89502. Annual Meeting: 1983—date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. Annual Meeting: 1983—date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: November 3-5, 1982, Thunderbird, Jantzen Beach.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: September 14-17, 1982, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 7-10, 1982, Towne Motel, Yakima.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 30-July 3, 1982, Jackson Lake Lodge, Moran.

(Continued from Page 54)

July 29-30—**Infertility.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

August 19-21—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

September 8-15—**13th International Cancer Congress.** Seattle. Wednesday-Wednesday. Seattle Center. Contact: Congress Operations Office, 13th International Cancer Congress, Fourth and Blanchard Building, Suite 1800, Seattle, WA 98121. (206) 621-9440.

September 16-18—**(WYOMING) Cytology Continuing Education Workshop.** Jackson. Thursday-Saturday. Contact: CME Harborview.

September 22-24—**Internal Medicine Review.** Seattle. Wednesday-Friday. Park Hilton. Contact: U/W.

September 23-25—**Cytology Continuing Education Workshop.** Renton. Thursday-Saturday. Valley General Hospital. Contact: CME Harborview.

October 7-10—**Annual Meeting, Washington State Medical Association.** Yakima. Thursday-Sunday. Yakima Convention Center, The Towne Plaza, and The Holiday Inn. Contact: Marcia Wahlman, Convention Coordinator, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

November 11-12—**Topics in Emergency Medicine.** Seattle. Thursday-Friday. Sea-Tac Marriott Hotel. Contact: Heidi Hilby, Executive Secretary, Washington Chapter, American College of Emergency Physicians, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

February 14-17—**(IDAHO) Sun Valley Primary Care Conference.** Sun Valley. Monday-Thursday. Sun Valley Lodge. Contact: Marilyn R. Carlson, Continuing Education, Northwest Hospital, 1551 North 115th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

WYOMING

June 30-July 3—**Wyoming Medical Society Annual Meeting.** Moran. Wednesday-Saturday. Jackson Lake Lodge. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne. WY 82001. (307) 635-2424.

See Utah Listing, July 21-25.

See Washington listing, September 16-18, 1982.

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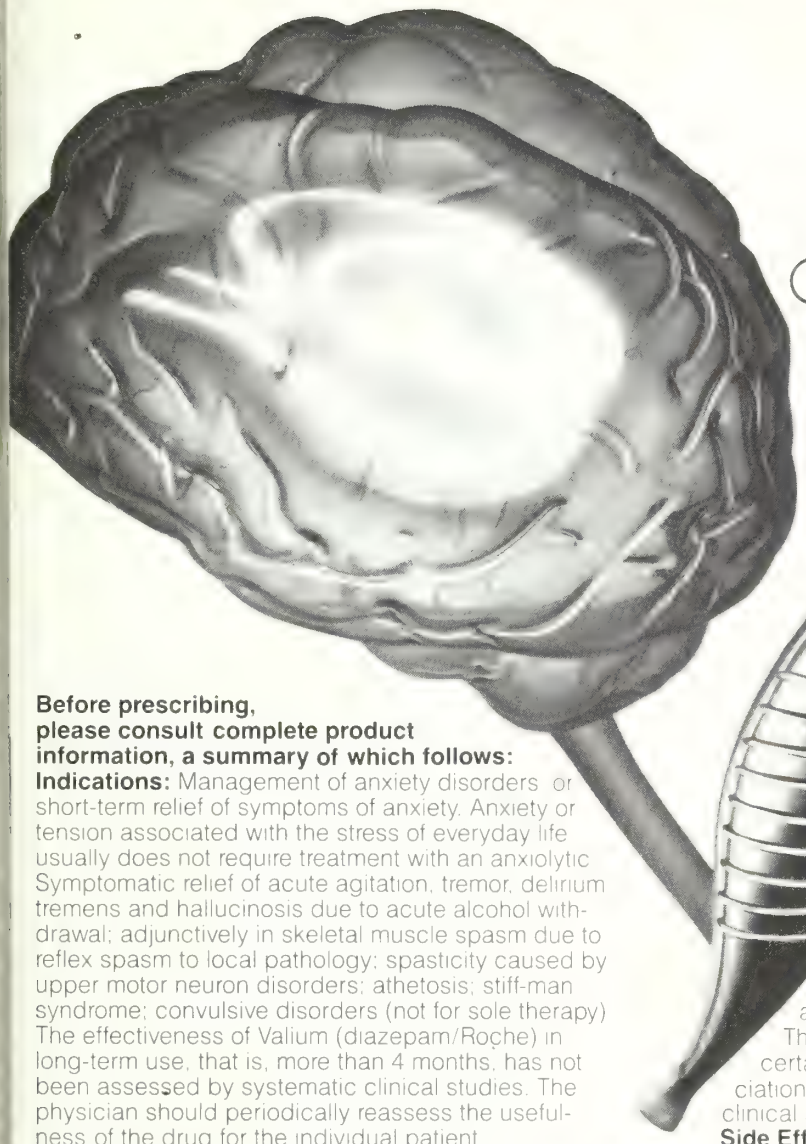

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

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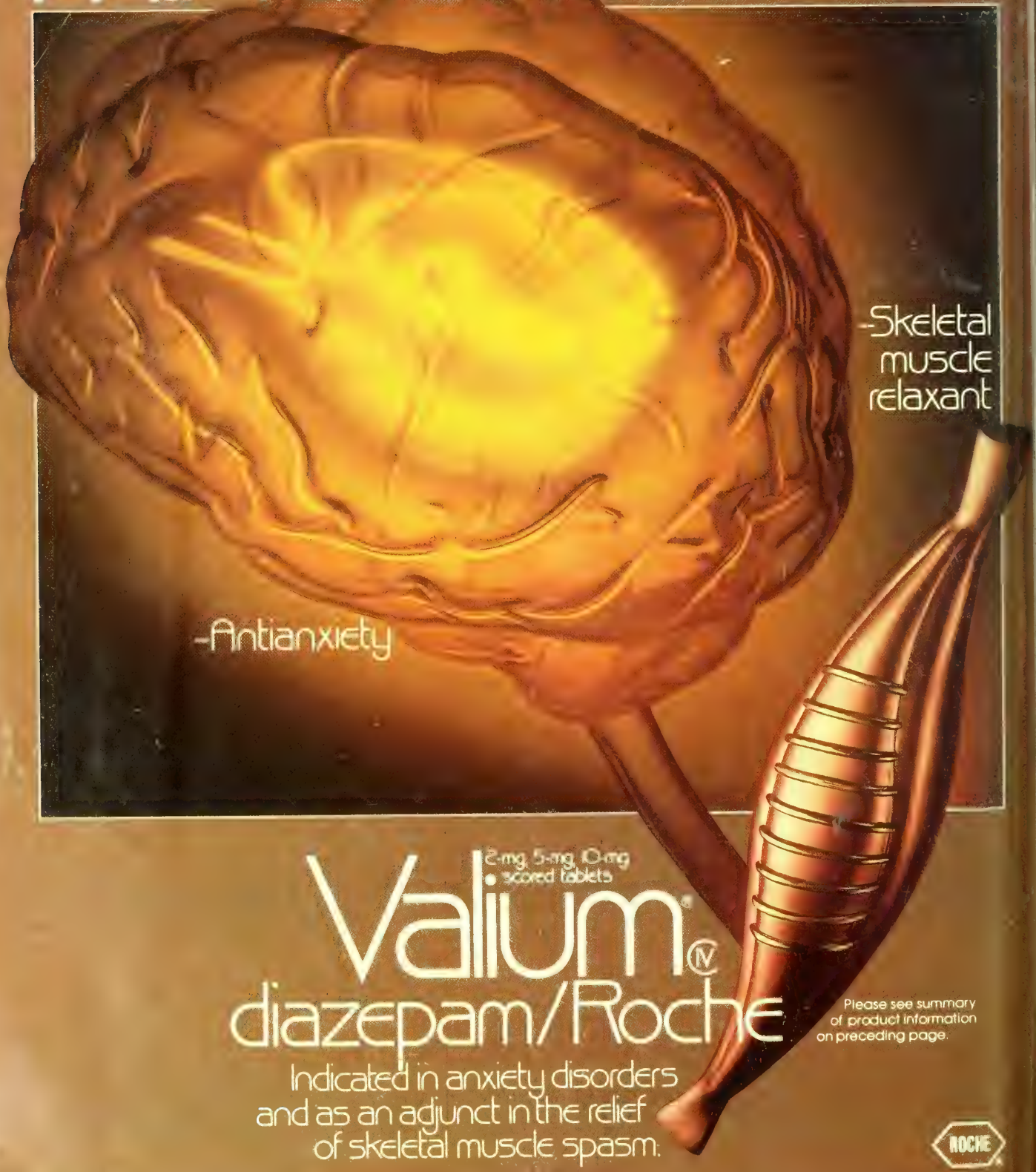

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